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PREMATURE CONTRACTIONS ARISING IN THE JUNCTIONAL TISSUES

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With Plate 1

PREMATURE contractions arising in the junctional tissues are comparatively rare in patients. Instances in which beats are supposed to have arisen in the neighbourhood of the auriculo-ventricular node have been reported by Mackenzie (8) and Hering and Rihl (4), and the localization in these examples was arrived at by means of polygraphic curves. A solitary clinical example of the electro-cardiographic curves of nodal beats was given in an earlier publication (6); the case was one in which paroxysms of tachycardia occurred, and in which auricle and ventricle beat simultaneously. James and Williams (5), in their general paper on electro-cardiograms, have published a figure which is probably from a case of premature beats arising in the node. The localization of nodal beats in the past has depended in the main upon the recognition of simultaneous and premature contraction in both auricle and ventricle, the instants of onset of contraction in one or other chamber being fixed by means of polygraphic curves. Similar heart mechanisms have been observed in experiment, and have been published by Lohmann (7), Hering (2), Rothberger and Winterberg (9) and myself (6). The mechanism in premature beats of the form considered is not entirely clear, and chiefly on account of the difficulty of ascertaining the rates of transmission through the node and bundle in one or other direction. Recent observations by Hering (3) seem to show that the chief delay in transmission occurs in the node itself, and consequently that if (a) the intervals between onsets of auricular and ventricular systole are reduced in the premature beats, or if (b) the two systoles are quite simultaneous, or if (c) the ventricular systole slightly precedes the auricular, then the premature impulse has arisen in the node or its immediate neighbourhood and has given rise to coincident or partially coincident contractions in the upper and lower chambers.

At the present time, chief interest centres in the electro-cardiographic curves associated with heart contractions of this form. If a contraction impulse starts in the node or in the main bundle, it travels to the ventricle through the normal paths, and consequently the ventricular contraction may be

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[1] Working under the tenure of a Beit Memorial Research Fellowship.

expected to be of normal type. The electric complex corresponding to it should have approximately the form given by the rhythmic beats in the same case. When the ventricle contracts prematurely and the electric complex corresponding to it is of normal outline, or more correctly when it has an outline similar to that of the ventricular complex of the rhythmic beats in the same case, the impulse which gives rise to it is of supraventricular origin; that is to say, it starts in the auricle, in the auriculo-ventricular node, or in the bundle up to the point of its division. The form of the premature ventricular complex consequently gives an immediate clue to the chamber or tissue in which the impulse has arisen.

The accompanying curves were taken from a case of aortic regurgitation. Fig. 1 shows electro-cardiograms from the three usual leads, right arm to left arm, right arm to left leg, and left arm to left leg; each strip presents a single premature contraction of the ventricle, and in each instance the ventricular complex of the premature contraction is similar in form to the complexes corresponding to rhythmic beats. It may consequently be concluded that *the impulse giving rise to these premature contractions originated in a supraventricular focus.*

The second point to be noted in the curves is the absence of disturbance of the auricular rhythm. The pause following each premature beat is always fully 'compensatory',[2] and in the majority of the curves the sequential P summit, i. e. the auricular contraction which fails to yield a ventricular response because its impulse falls in the refractory period of the ventricle, is plainly visible. For example, it is seen in the second strip of Fig. 1, and precedes the small upstroke R of the premature ventricular complex. The ventricle has not responded to this auricular contraction, for the corresponding P–R interval is curtailed. In the third lead the commencing upstroke of P is seen, and is succeeded almost immediately by the small upstroke R of the premature ventricular complex. In this instance the P–R interval is reduced from the normal length, 0·16 sec., to 0·04 sec. In the first lead the sequential auricular contraction falls with R of the premature ventricular complex and is not visible. The conclusion from these findings, namely, the absence of disturbance of auricular rhythm and the absence of relationship between the time of onset of auricular and ventricular contractions, is clear. The premature contractions have had little or no influence upon the sequential auricular contraction. *Therefore they have arisen at some point below the main mass of auricular musculature.*

The two main conclusions may be combined in the statement that the point at which the premature contractions originate lies between auricle and ventricle, and either in the auriculo-ventricular node or in the bundle before its division.

Now the accumulated evidence goes to show that a premature impulse arising in the node will give rise to a premature contraction in both auricle and ventricle, while a single premature contraction arising in the ventricle rarely, if

[2] Sometimes the pause is slightly increased beyond this, as a result of an accompanying sinus slowing.

ever, passes back to the auricle. There is always some obstruction to the occurrence of a single retrograde beat, and it appears as if this obstruction is mainly in the auriculo-ventricular node. When a supraventricular impulse fails to affect the sequence of auricular contractions, as in this case, we are tempted to conclude that such an impulse has arisen below the node itself, that is to say in the main bundle. In the present instance the conclusion would be more justifiable were it not for the curious relationships of the commencements of auricular and ventricular systoles. The sequential auricular complex P usually precedes the commencement of the premature ventricular complex (second and third leads of Fig. 1), and it may be held that the auricle has failed to respond because the impulse travelling upwards has encountered an auricular impulse travelling downwards; or that (in the first lead) the auricle is in contraction and its muscle is refractory when the impulse reaches it. In no observed instance, in this patient, has the auricular contraction fallen so far ahead of the upstroke of R that the last possibility can be absolutely excluded. But it has fallen sufficiently ahead of it (Fig. 2) to render it probable that the point at which the impulse of the premature contraction arises lies at some distance from the auricle.

These considerations make it probable that we are dealing with an instance of premature beats arising in the auriculo-ventricular bundle rather than in the node itself.

Note. The type of ventricular contraction found in this case corresponds to that described as characteristic of hypertrophy of the left ventricle, a fact in accordance with the presence of aortic regurgitation. In Fig. 1, lead I, R is increased, in lead III R is markedly diminished and S greatly exaggerated. (See Einthoven (1).)

Summary.

1. An instance of premature contractions arising in the junctional tissues is described. The impulses probably originated in the auriculo-ventricular bundle.

2. Premature contractions arising in the junctional tissues do not necessarily affect the auricular rhythm.

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EXPLANATION OF FIGURES.

Fig. 1. (× $\frac{5}{7.5}$.) Three electro-cardiograms from a case of aortic disease. Each strip in this figure shows a single premature contraction. *I*, lead from right arm to left arm ; *II*, lead from right arm to left leg ; *III*, lead from left arm to left leg. The premature ventricular complex closely resembles the complex of the regular beats in each lead. The auricular beats (*P*) occur at regular intervals throughout the curves.

Fig. 2. (× $\frac{5}{7.5}$.) Lead from right arm to left arm in the same case. The sequential auricular contraction (*P*) falls in the centre of the premature ventricular complex.
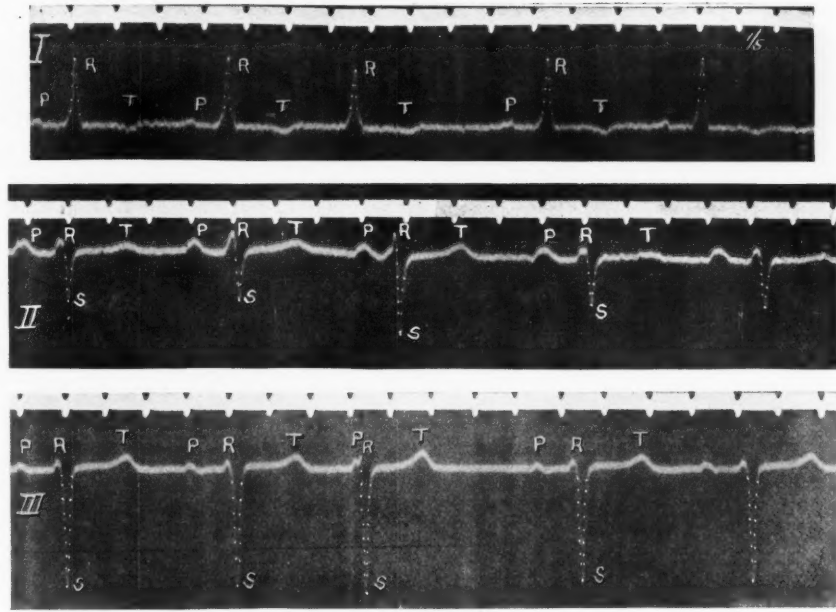
FIG. 1
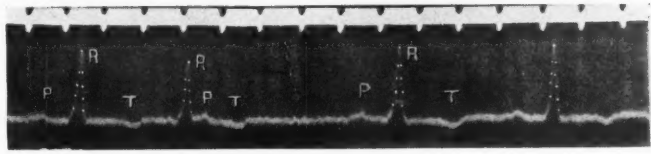
FIG. 2

PAROXYSMAL TACHYCARDIA ACCOMPANIED BY THE VENTRICULAR FORM OF VENOUS PULSE

By THOMAS LEWIS [1] AND M. D. SILBERBERG

(From University College Hospital Medical School)

With Plate 2

A HOUSEWIFE, aged 23, was admitted to University College Hospital on April 10, 1911, complaining of attacks of palpitation. The observations made upon her are of importance in that they help in elucidating an obscure form of paroxysmal tachycardia.

Family history. Her mother died of phthisis at the age of 38. Her father died of 'heart disease'. One sister died of phthisis, one from diphtheria; there were three brothers living, one had had acute rheumatism, two were healthy. She had a baby 14 days old. The husband was healthy.

Personal history. She was in domestic service before marriage (eighteen months ago), but gave it up because she could not manage to climb stairs, as it brought on shortness of breath. The bowels had been regular, she slept well, and her appetite was good. Menstruation was regular before pregnancy. There had been no miscarriages.

Previous illness. She was not strong as a child, suffering from enlarged tonsils, sore throats and rheumatic fever; the first attack of fever was at 8 years of age, the next attack at the age of 11 years. She was treated at Great Ormond Street Hospital on both occasions.

Present illness. She stated that she had suffered from attacks of palpitation since she was 14 years of age. From 14 to 16 they were infrequent, occurring about once in six months. At 17 years of age they appeared more frequently, and generally just before the onset or just at the cessation of the menstrual periods. After this they became less frequent, occurring about once in nine months, till four months ago. At this time she was five months pregnant and attacks were very frequent; she experienced as many as four or five attacks a week. She said that excitement or slight exertion might bring on an attack. There was no warning of the attack, except perhaps a lump in the throat; the onset was abrupt and often unexpected. She felt suddenly helpless and faint, but did not fall; she could not lie down, preferring to sit or stand. There was difficulty in speaking because of a choking sensation in the throat, which she said was due to the rapid throbbing in the vessels of the neck. She felt her heart to be palpitating and said that during the progress of the attack her heart felt as if it were moving to the left and growing bigger. When her heart seemed as if it were right round under the armpit, she had a slight dull aching pain in this situation. At these times she had great difficulty in breathing and thought she was taking her last breath and about to die. She said she felt as if she could not get her breath out of her chest because her heart was beating so quickly. She could walk about in the attacks, and often preferred to do so because

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[1] Working under the tenure of a Beit Memorial Research Fellowship.

she found that the palpitation gradually quietened down; if she lay down, she was often more helpless and weaker than when sitting; the palpitation increased and the breathing was more distressed. Although she preferred to walk, and could do so without assistance, she was quite incapable of performing even the slightest exertion (climbing one stair, &c.). The attacks varied in duration from ten minutes to a day and a half. In practically all the attacks she brought up a lot of wind, and with this some green vomit. Vomiting nearly always stopped the attack. She said that, if the vomiting did not occur spontaneously, she induced retching by 'sticking her finger down her throat', and that this was often effectual. She had observed that an attack might start as a result of turning on to either side when in bed, or as a result of stooping suddenly; some of them had waked her from sleep. When she was younger, a hard day's work was frequently followed by an attack during the next day. While she was pregnant, the attacks were most frequent and occurred daily. Since the child was born (fourteen days previously) she had had three attacks, two attacks lasting a day and one short one of about an hour's duration. At the termination of the attack she felt a hot flush all over, sweated freely and was momentarily giddy. She said that the heart seemed to stop still for a moment and then resumed its ordinary beating, or she might feel three or four big thumps and then the ordinary regular beat again. The termination brought a marked sense of relief, and she was at once capable of setting about her household duties as if nothing had happened. Afterwards people told her that her eyes were puffy.

Physical examination, April 28, 1911. She was a fairly well-nourished woman and had a somewhat pallid complexion. Temperature 97–98°. Pulse 72 and regular. The arteries showed no thickening and the pulse was of good volume.

The heart's dullness lay $\frac{3}{4}$ and $4\frac{1}{4}$ inches to right and left of the mid-sternal line when she was supine. The impulse was palpable in the fifth space. A diastolic thrill was palpable over the apex. At the apex, a systolic murmur and a well-marked diastolic murmur, not quite filling the whole of diastole, were heard. The second sound was well marked. The mitral systolic was conducted into the axilla, the diastolic was conducted only between apex and third interspace. At the base, the second pulmonary sound was accentuated and reduplicated, and the aortic sounds were clear.

Occasional sibilant rhonchi were heard over the right apex, but no crepitations. There was no impairment of the percussion note. There were some signs of emphysema. The liver was just palpable.

Notes of the attacks. Attacks of tachycardia were observed on several occasions. There was a paroxysm on April 13 (three days after admission), which lasted for more than fifteen hours; during it venous curves were obtained. A shorter attack, of about two hours' duration, occurred on the 18th, and on the 23rd she had an attack lasting eight hours, during which electro-cardiographic curves were obtained. On the 27th there was a brief attack in the night; on the 29th she woke 'with palpitation'. The paroxysm lasted twelve hours and, as in previous experiences, ended quite suddenly. Speedy relief from symptoms always accompanied the offsets.

During the long paroxysm of April 13, and towards its termination, examination showed the condition to be critical. The patient was very pallid and cyanosed, and presented a trace of jaundice. The breathing was very distressed; respirations were at the rate of 40–50 per minute. The pulse varied from 180 to 200 per minute. The right and left margin of the heart's dullness lay $2\frac{1}{2}$ inches to the right of the mid-sternal line and in the mid-axillary line respectively. The liver reached to the umbilicus, was hard, tender and pulsating. A number of remedies were tried without avail; for example, injections of digalen (10 minims) and strophanthine (1/250 grain). Ice packs were applied to the chest and vagal compression was repeatedly tried, but the attack continued until several hours later it terminated with the onset of vomiting.

Polygraphic Curves.

The venous curves taken during the slow heart periods show the mechanism to be sequential; the *a–c* interval is a full 1/5 second in Fig. 1. During the paroxysms the ventricular form of venous pulse appeared (Fig. 2) and accompanied a regular radial pulsation at from 180 to 200 per minute. The jugular
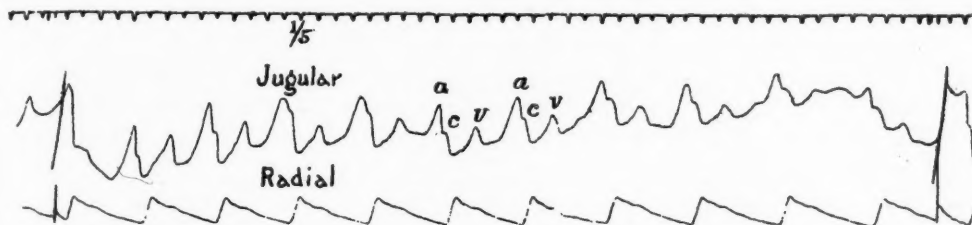
FIG. 1. A polygraphic curve taken while the heart action was normal in sequence and rate. Each radial cycle is accompanied by *a*, *c*, and *v* waves in the corresponding jugular cycle. The rate is 190 per minute.
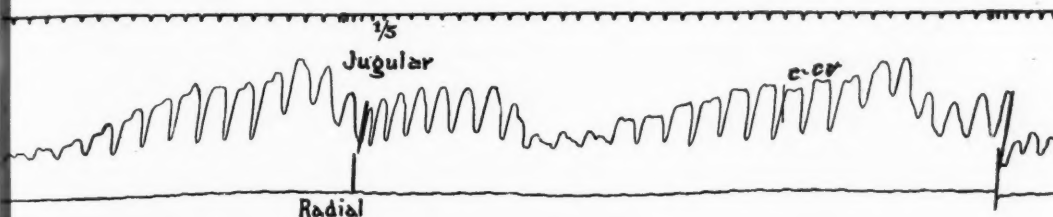
FIG. 2. A polygraphic curve taken during a paroxysm. Each radial cycle is accompanied by a plateau in the jugular curve, which plateau fills the systolic period. The rate is 61 per minute.

curves taken during the paroxysmal stage throw little light upon the actual mechanism present. The regularity of the radial tracing indicates the origin of the paroxysm from a single point in the heart musculature—a conclusion which is borne out by the electric findings.

Electro-cardiographic Curves.

The paroxysmal curves (Fig. 3, *IV*, *V*, and *VI*) were taken during the attack which occurred on April 23. The normal mechanism was present on the succeeding morning, and the corresponding curves (Fig. 3, *I*, *II*, and *III*) were then secured.

Curves *I* and *IV* represent leads from right arm to left arm, *II* and *V* are from right arm to left leg (these are standardized), *III* and *VI* are from left arm and left leg. The marks on the right-hand margin of curves *II* and *V* represent the deflexion obtained by throwing in 1/1,000 volt, with the patient in circuit and the string at the sensitivity employed for the observations.

As is so usual in cases of paroxysmal tachycardia, the ventricular complexes of the curves from paroxysmal and slow periods show a close resemblance. The similarity in the right arm to left leg leads (I and IV) is most striking, though S is increased during the paroxysm. In the right arm to left arm lead of the paroxysm (V) T is partially inverted and R shows an absolute increase. In II the calculated value of R is 0·0019 volt; in V its calculated value is 0·0025 volt. This increase in R during the paroxysmal stage has been previously recorded, and it seems to be comparable to the occasional increase of R in the ventricular complex of premature auricular contractions. The latter is also frequently associated with partial inversion of T, as in this case. In the left arm to left leg lead T is partially inverted during the paroxysm (VI), while it is upright during the slow heart action (III).

The comparison of the outlines of the ventricular complexes, when fast and slow heart actions are present, clearly establishes the supraventricular origin of the paroxysm itself. They are complexes corresponding to beats which are started by impulses descending along the normal channels. The paroxysms have their origin, therefore, in auricle, auriculo-ventricular node or main bundle.

When attention is turned to the auricular representatives, the increased value of P, its broad and bifurcated summit, are indications of the auricular hypertrophy, and are compatible with the remaining clinical signs of mitral stenosis. The exaggeration of R in the left arm to left leg leads, and the diminution of R and exaggeration of S in the right arm to left arm leads, are indications of right ventricular hypertrophy and are equally consistent with the diagnosis of mitral stenosis.

The auricular complexes are conspicuous during the slow heart action. They are not to be found during the paroxysmal stage, and this fact is attributed, as it has been in previous cases, to the ectopic origin of the corresponding rhythm. The auricular complex is supposed to be isoelectric or nearly isoelectric, and its position consequently cannot be fixed in these curves. The P–R interval of the slow periods is 0·19 sec. The P–R interval of the paroxysmal stage is necessarily unknown.

The electric curves show no trace of those oscillations which are known to consort with fibrillation of the auricle, a condition which may therefore be excluded. The constancy in the type of complex from cycle to cycle, and the regularity of the sequence, demonstrate the origin of the paroxysm from a single focus in the heart muscle.

Summary.

1. A case of paroxysmal tachycardia is described, in which during the attacks the ventricular form of venous pulse was present. The paroxysms were of supraventricular origin, and probably arose as an ectopic rhythm from some portion of the auricular musculature.

2. The summit R, during the paroxysm, showed an increase of 0·0006 volt over the summit R of the slow periods, in the right arm to left leg lead. This increase of R is a common feature of paroxysmal tachycardia, as is also an accompanying decrease or inversion of T.

DESCRIPTION OF FIGURE.

FIG. 3. (× ⅔.)   A series of electro-cardiographic curves, of which I, II and III were taken while the heart rate was within the normal limits, and of which IV, V and VI were taken during a paroxysm. I and IV were taken by means of a lead from the right arm to the left arm ; II and V by means of a lead from right arm to left leg ; and III and VI by means of a lead from left arm to left leg.

These curves show :—(1) The large P summit of the slow period, which is so characteristic of auricular hypertrophy ; (2) a decrease of R in I, an increase of R in III, which is a common feature of right-sided ventricular hypertrophy ; (3) the similarity of the ventricular complexes during the slow and fast mechanisms, proving the supraventricular origin of the paroxysms ; (4) the absence of a defined P summit during the paroxysm, suggesting that the latter arises ectopically ; (5) an absolute increase of R during the paroxysm (compare II and V in which $\frac{1}{1000}$ volt gives a similar deflexion) ; (6) partial or complete inversion of T during the paroxysms in the second and third leads.
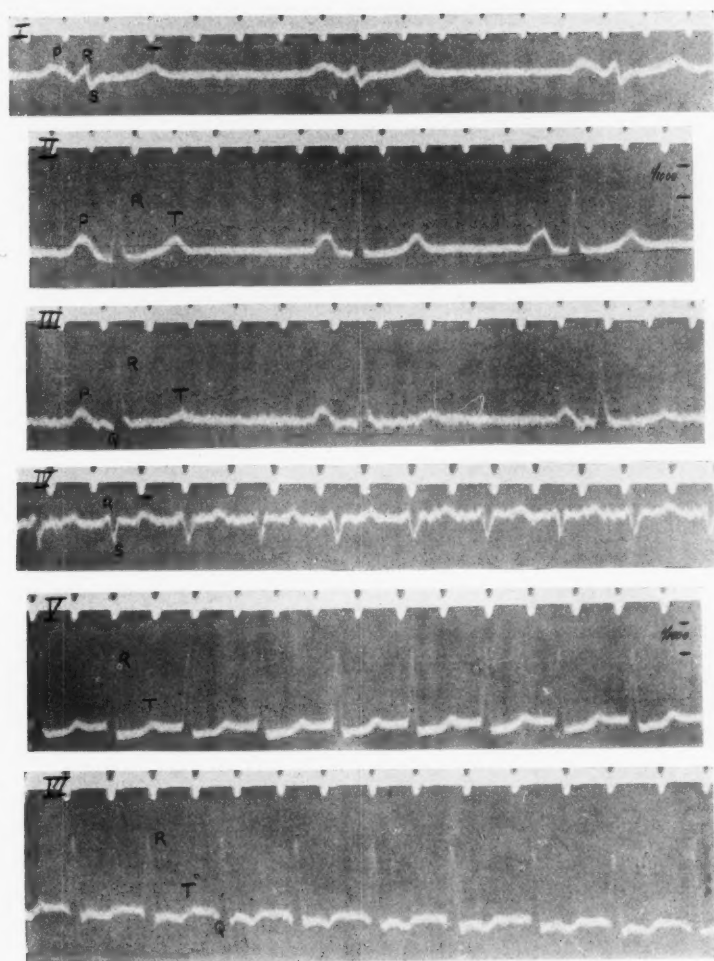
Fig. 3

THE ORIGIN OF THE ELECTRIC OSCILLATIONS AND THE DIRECTION OF CONTRACTION OF THE VENTRICLE IN INSTANCES OF COMPLETE IRREGULARITY OF THE HEART (AURICULAR FIBRILLATION)

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With Plates 3 and 4

In the present communication it is my desire to bring forward further evidence of two propositions. First, that the oscillations, which are so prominent in the electric curves of patients who exhibit complete irregularity of the heart, are produced in the auricular portion of the heart. And second, that the contraction wave takes the same course in the ventricle when complete irregularity is present and when the heart's mechanism is undisturbed, the ventricle responding regularly to auricle. A good deal of evidence has already (*Heart*, 1909–10, i. 306) been brought forward in support of each of these propositions. Thus, it has been shown that the oscillations referred to are independent of somatic muscle contraction and that, when the galvanometer which records them is connected to the patient by means of direct chest contacts, a lead from the vicinity of the right or superficial auricle yields maximal oscillations. It is also needful to demonstrate that, when direct chest leads are utilized, the occurrence of maximal oscillations in a lead from the vicinity of the right auricle is confined to cases of complete irregularity, and that this same lead also gives a large excursion at each contraction of a co-ordinately beating auricle.

Again, it has been demonstrated that in cases of complete irregularity the ventricular electric complex is of a type which is recognized as compatible with a contraction of the ventricle in response to auricle, that is to say with a contraction of the ventricle arising in a *supraventricular* impulse. For, when complete irregularity is present, each ventricular systole is accompanied by an R summit, and frequently by a summit T. The complete evidence required to substantiate the view that the direction of ventricular contraction is the same when the heart mechanism is normal and when the ventricle is irregular, is only to be obtained by securing the pictures given by a series of separate leads, and by a comparison of these pictures when one or other mechanism is present *and in the same subject*.

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[1] Working under the tenure of a Beit Memorial Research Fellowship.

Observations.

The three leads originally devised by Einthoven, and now very generally adopted for clinical work, are shown in Fig. 1. The galvanometer is connected respectively to—

  I. Right arm and left arm.

  II. Right arm and left leg.

  III. Left arm and left leg.[2]

In each instance the first contact named represents that portion of the body which is connected to the lower end of the galvanometer string. For the purposes of the present observations I have utilized certain additional leads. They are :—

  IV. Sternum at second cartilage and inner end of fourth right interspace.

  V. Sternum at third cartilage and inner end of fifth right interspace.

  VI. Outer end of third left interspace and apex beat.

  VII. Epigastrium and apex beat.

  VIII. Sternum at second cartilage and apex beat.[2]

Copper disks $1\frac{3}{4}$ inches in diameter are used as contacts, and they are fastened to the chest by a stiff paste composed of flour, salt, and water.

The patient who was the subject of the observation suffered from shortness of breath on slight exertion and occasional swelling of the legs as a result of dropsy. The measurements of cardiac dullness in the supine posture were as follows :—Upper limit, third interspace ; right limit, $1\frac{1}{4}$ inches to right of mid-sternal line ; left limit, fifth space, $5\frac{1}{2}$ inches from the mid-sternal line. A systolic murmur was present at the apex, but no other physical signs were found in the heart.

The two series of observations recorded at the present time were made on the 4th and 17th of May, 1911. On the 4th the heart's mechanism was normal. On the 17th complete irregularity of twenty hours' duration was present. The area of heart dullness appeared to be the same on the two occasions. Both on the 4th and on the 17th a complete series of curves was obtained from the separate leads ; those of the 4th are shown in Fig. 2 ; those of the 17th are shown in Fig. 3. The two series of curves are placed side by side, the corresponding strips lying opposite to each other, so that comparison is facilitated, and the strips are numbered to correspond with the diagram of leads (Fig. 1).

In all the curves of Fig. 2 the beats are regularly spaced. In all those of Fig. 3 the irregularity is complete. The representative of auricular contraction (*P*) is present in greater or lesser degree in each strip of Fig. 2 ; it is absent in all the strips of Fig. 3, and is replaced by irregular oscillations of greater or lesser amplitude in each.

Considering the direct chest leads of Fig. 2 (*IV–VIII*),[3] *P* is most prominent

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[2] Baths of salt solution in which the limbs are immersed are used as contacts.

[3] It is to be observed that, although amplitude is compared, the curves referred to are not fully standardized. The comparison is between one chest lead and another in a given series,

in strip V, the lead from sternum at third cartilage to inner end of fourth right interspace, and this is the lead which is in closest proximity to the right auricle. It is also well seen, though it is less marked, in leads IV and $VIII$; it is just perceptible in leads VI and VII.

Considering the direct chest leads of Fig. 3 (IV–$VIII$) the oscillations (f) are maximal in lead V, are clearly visible in leads IV and $VIII$, and are just visible in leads VI and VII.
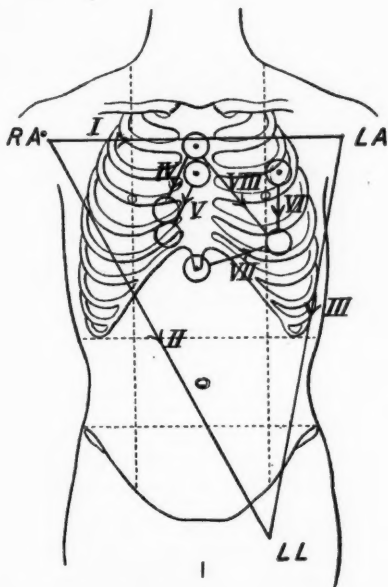
Fig. 1. A diagram showing the leads adopted in the recorded observations. I, II and III are the three leads adopted by Einthoven; RA = right arm; LA = left arm; LL = left leg. Leads IV–$VIII$ are taken from fixed points on the chest wall, and are utilized in obtaining the purest pictures of auricular and ventricular electric effects.

The comparison between the two series of chest leads shows that the lead which gives the most prominent P summit, while the heart mechanism is normal, likewise yields the maximal oscillations when the heart is irregular. And the comparison may be extended to the whole series. The largest oscillations are shown in Fig. 3, II and III, the tallest P summits in Fig. 2, II and III; in Fig. 3, I, the oscillations are somewhat less prominent, in Fig. 2, I, P is less pronounced.

We consequently arrive at the conclusion that *when complete irregularity*

and the single possible variant is the resistance of tissue in one or other lead, for the same electrodes were employed from lead to lead and the string sensitivity remained constant throughout. Considering that the remaining resistance in circuit was approximately 10,000 ohms, any small variations in skin resistance from point to point are obviously negligible in so far as the main argument is concerned.

of the heart is present, the amplitude of the oscillations, in any given lead, is in *proportion to the amplitude of 'P' in the same lead when the heart mechanism* *is normal.* It is upon this conclusion that we may now base the assertion that the electric oscillations, recorded when the heart is completely irregular, are of auricular origin.

We may now turn to the second proposition, i. e. that which deals with the direction in which the ventricular contraction is propagated. The object of clearly demonstrating that the direction of contraction is the same, while normal mechanism is present and while the heart beats in a completely irregular fashion, will be evident. Under the former circumstance the ventricle receives its impulses from the co-ordinately beating auricle, and it is desirable to show that it receives its impulses from the auricular tissue under the last-mentioned condition. The proof of similar direction of contraction rests upon a careful comparison of the ventricular portions of the curves shown in the corresponding strips. In Fig. 2, *I*, the ventricular complex consists of *Q*, *R* and *T* summits. These are also present and have a similar outline in Fig. 3, *I*. In Figs. 2, *II*, and 3, *II*, *Q*, *R*, *S* and *T* summits are seen and again the outlines are similar. In Fig. 2, *III*, *R* is small, *S* is deep and has a slight notch on the downstroke; the same features are found in Fig. 3, *III*. A comparison of the direct chest leads (*IV–VIII*) is equally convincing; summit for summit the curves correspond, and they differ solely in minor changes of amplitude, and in the fact that in the curves of Fig. 3 the inconspicuous and broad summits of the later phases of systole are distorted in some measure by the oscillations.

We may conclude, therefore, that *the electric changes of the ventricle shown* *by a series of leads from fixed points are qualitatively identical, whether such* *leads are taken when the heart mechanism is normal, or whether they are taken* *at a time when the ventricle is completely irregular.* And this conclusion confirms the previously adopted view that when the heart is affected by this specific disorder of its mechanism the impulses reach the ventricle from a supraventricular source.

The two main contentions, the origin of the oscillations in the auricle and the passage of the impulses which originate ventricular contractions along the normal channels, in patients who are the subject of ventricular irregularity, are in every way compatible with a previously expressed conclusion that in such patients the auricle is in a state of fibrillation.
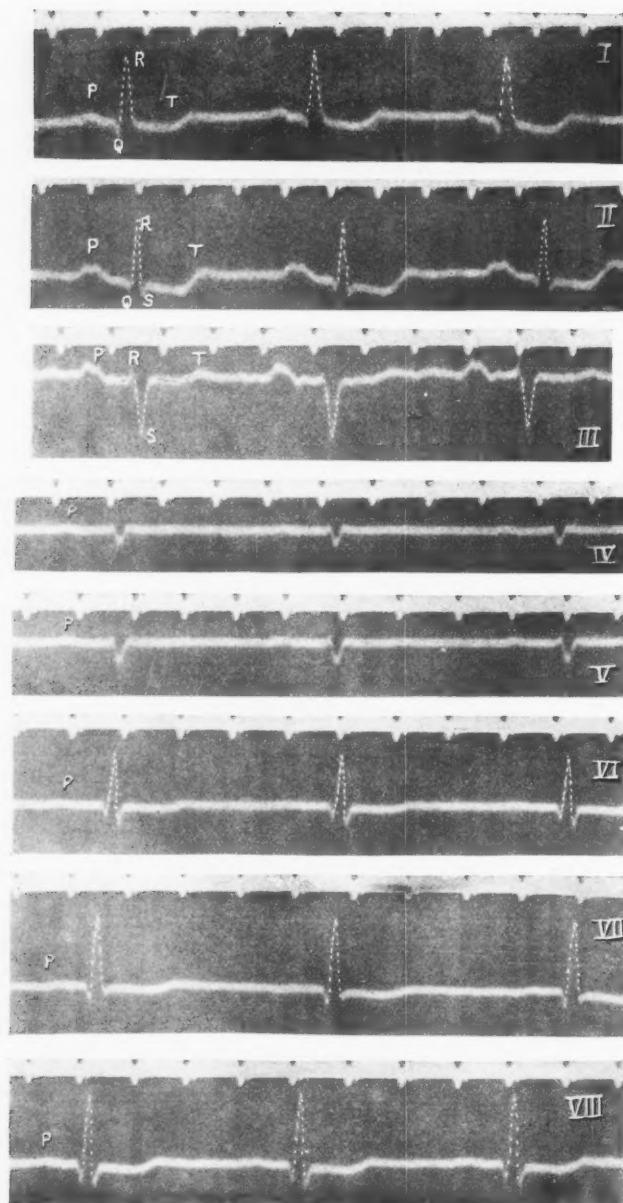
FIG. 2
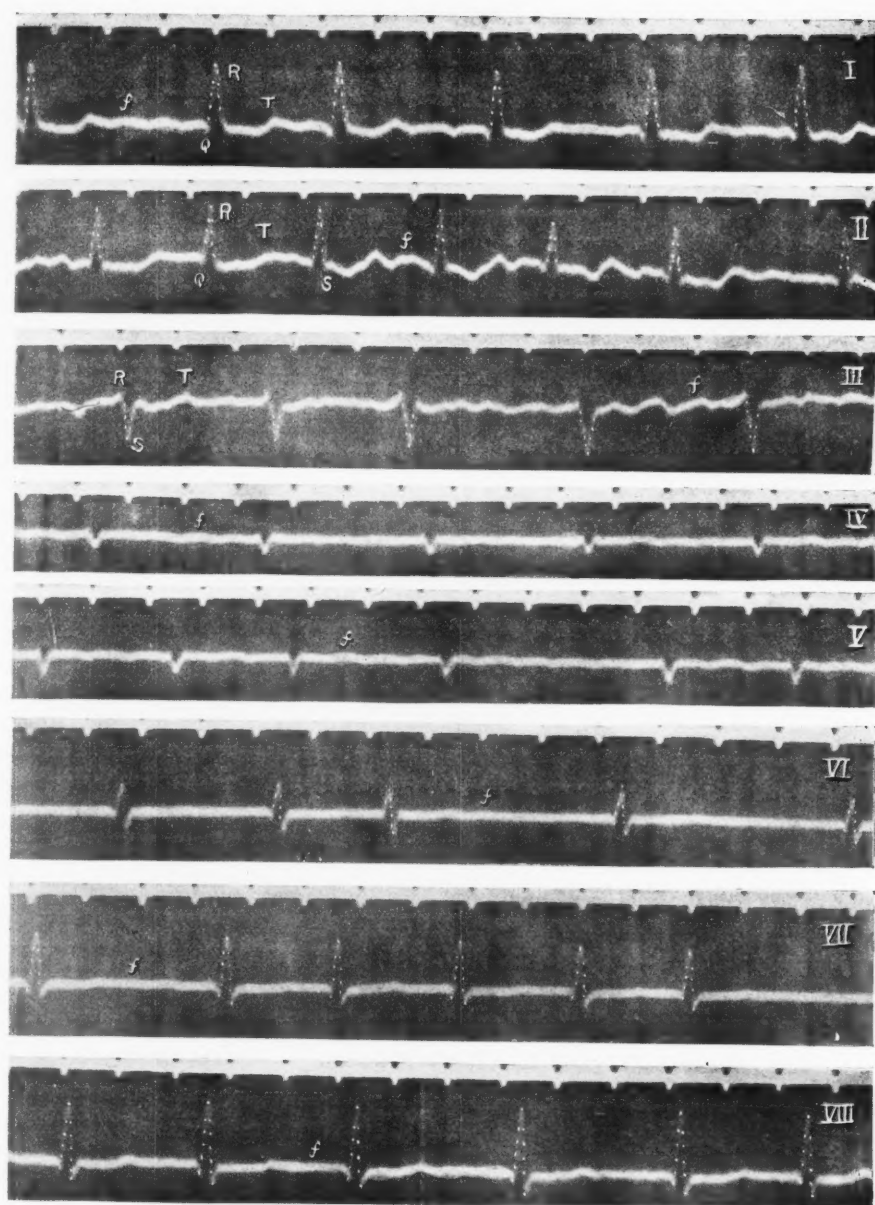
Fig. 3

A STUDY OF SOME FACTORS IN THE AETIOLOGY OF ORAL CARCINOMA

By CHARLES SINGER

(From the Research Institute, Cancer Hospital, London[1])

I. *Introduction.*

THE impetus given to the investigation of carcinoma by the improved technique of experimental methods and the important discoveries resulting therefrom has tended to withdraw attention from more traditional lines of research.

And yet perhaps of no condition is it more true than of cancer that the patient has to be considered as well as the disease, and in none has research pointed more clearly to the existence of biological factors in the patient himself, influencing the onset and course of the morbid process.[2] Valuable, therefore, as experimental investigation on animals will doubtless prove in the search for the exciting factors of carcinoma, it seems less likely that this method will yield results of the same moment as regards predisposing causes. For the preliminary investigation of these, we may rather look to the physical endowment and condition of the human subjects of the spontaneous disease, in whom individual differences are more easily observed and their connotation better understood.

During two years the writer has devoted much time to the investigation of the general physical and diathetic states of carcinomatous patients. Each case has been subjected to a thorough examination, such as would be undergone by one applying for a policy of life assurance, comprising an inquiry into details of general habits of life and of previous illnesses, as well as an investigation into the general physical condition. About 700 cases have been thus examined, and the clinical material traced into the laboratory and the post-mortem room.

[2] In justification of this statement attention may be drawn to the greater success of auto-inoculation as against hetero-inoculation in rodents, to the importance of the age factor in judging the suitability of animals for inoculation experiments, and to the varying susceptibility to inoculation of different stocks of mice.

In the following pages attention is especially directed to carcinoma arising in the mucous membrane of the oral cavity ; other forms of cancer have, however, been freely used for purposes of comparison and ' control '.

II.   *The General Physique of the Subjects of Oral Carcinoma.*

That there is a definite type of physique associated with cancer has not been generally admitted. The writer is, however, under the impression that cases of *oral* carcinoma present a larger proportion of robust, full-blooded, strong, heavy subjects than is found among the general population of the same age.

The term ' impression ' is used because it is extremely difficult to give to such a sta tement any numerical value.   The data, however, seem to bear out an opinion current among surgeons and anaesthetists that cases of carcinoma linguae are by no means good subjects for operation; that as a class they take anaesthetics very badly (even allowing for the mechanical difficulty of administering chloro- form in an oral operation); and that tracheotomy, when it has to be performed, often presents special difficulty, owing, among other reasons, to the shortness of the neck and the strength and refractoriness of the patient.

On the whole the past general health of cancerous subjects appears to have been excellent. In answer to questions concerning past diseases, the patients reiterate one after the other with wearisome monotony, 'I have never had a day's illness in my life until this came on,' and thus seem to lay claim to a greater degree of physical vigour and robustness than can be professed by most ordinarily healthy people.   In the case of cancer of the tongue and other parts of the mouth it is thought that this freedom from general disease is even more marked than in the other forms of cancer here considered.

A very rough classification at most is all that can be attempted of so indefinite a term as ' robustness ', but a general analysis is here essayed of the physique of 100 cases of each of those forms of cancer of which the writer has adequate records :—

Health and Physique.	Oral Carci- noma.	Rectal Carci- noma.	Carcinoma of Cervix Uteri.	Mammary Carcinoma.
Very robust . .	71	62	45	21
Robust . . .	23	25	20	40
Fair	5	7	17	26
Poor	1	6	18	13
	100	100	100	100

Thus the degree of general vigour evinced by the subjects of oral cancer appears to be distinctly higher than that of the other categories, and is approached only by the rectal group. It is significant that the one case of oral cancer whose health, previous to the onset of the malignant growth, was really bad was a hemiplegic inhabitant of a workhouse infirmary, who had a cerebral haemorrhage at 45 and developed a carcinoma of the inner side of the cheek at 47 years of age.   He was a lead-worker, had suffered from syphilis and had had repeated attacks of gout, leaving tophi and other marks of its ravages

(see Appendix A, No. 68). This combination of syphilis, gout, and apoplexy, with oral carcinoma, forms a text which is enlarged upon in detail in the pages that follow.

Some numerical estimate of the degree to which the patients with carcinoma oris exceed others in robustness might perhaps be obtained by comparing their weights with those of the generality of the population. For this purpose the weights of a number of cancer patients were obtained immediately after admission to hospital. It is clear that there is a considerable fallacy here, by reason of the wasting effect of the disease itself, and yet, although several patients were in a very emaciated condition and scaled below 8 st., the average weight of thirty-eight consecutive cases of oral carcinoma was equal to or above the average for healthy men, being 10 st. 8 lb.[3]

A further suggestion as to the physical conditions in which oral carcinoma most frequently declares itself may be obtained from a consideration of the occupations of the subjects of new growths of that region. As the hospital population is admittedly drawn from a special social stratum, a fair view can hardly be obtained from that source. The returns, therefore, of a number of cases of death from cancer of the lip and of the tongue have been extracted from the death certifications for 1909 in the charge of the Registrar-General of England and Wales at Somerset House. The cases have not been selected, but were taken consecutively over a wide area of England and Wales, including both urban and rural populations, and the results are presented in the following table :—

TABLE I.

Males.	Percentage in 500 cases of Carcinoma of the Tongue.	Percentage in 132 cases of Carcinoma of the Lip.
Labourers and unskilled workers	25·0	25·8
Farm hands, ground labourers, and gardeners	6·6	47·7
Carpenters, joiners, and sawyers	4·5	5·2
Stable workers, coachmen, and ostlers	3·6	0·0
Artisans and mechanics	4·8	1·5
Railway servants	2·4	2·3
Butchers	1·4	0·0
Shop-hands	3·0	3·0
Clerical pursuits	1·9	0·0
Tailors	1·6	1·5
Professional and leisured	⎱ 7·2	0·0 ⎱
Painters, decorators, and lead-workers	15·8 ⎰ 4·8	0·0 ⎰ 1·5
Publicans and brewing trades	⎰ 3·8	1·5 ⎰
Blacksmiths, puddlers, and ironworkers	⎱ 3·6	0·0 ⎱
Sailors	5·8	0·8
Soldiers	15·4 ⎰ 4·0	3·0 ⎰ 3·8
Police	⎰ 2·0	0·0 ⎰
Miscellaneous	4·2	0·0
Females	9·8	7·7
	100·0	100·0

[3] Some writers (e. g. R. Schmidt, *Wien. med. Klin.*, No. 43, 1910) have endeavoured to demonstrate an antagonism between cancer and the infectious diseases of childhood. In the present writer's opinion the clinical method, applied mostly to ignorant hospital patients, is

Thus it appears that over 15 per cent. of those who died of cancer of the tongue were men who exercised trades for which special vigour would fit them, as police, farriers, soldiers, and sailors; while nearly 16 per cent. were either of the upper classes or followed occupations conducive to the development of gout, such as public-house keeping, house-painting, and lead-working, trades where, also, early arterial degeneration may be expected. The percentage, on the other hand, is conspicuously small of those who followed the professions usually assumed by the frailer portion of the population and in which good physical endowment is of no special advantage; thus, shop-hands, clerks, and tailors are poorly represented.

Turning now to the occupations of those who died from the apparently closely similar condition of cancer of the lip, it will be seen, firstly, that there is an overwhelming preponderance of outdoor labourers, who make up nearly half the total (47·7 per cent.), and, secondly, that there are comparatively few following those trades distinguished as predisposing to gout and arterial degeneration. Moreover, the percentage of those who followed the callings needing special physique falls far short of that met with in the lingual cases.

The analysis of the occupations of those who died of these two forms of cancerous disease thus reinforces the general impression that sufferers from cancer of the tongue are, as a group, peculiarly robust and vigorous individuals; while the old observation that carcinoma of the lip is especially common amongst the farm-labouring class receives further confirmation.

The preponderatingly rural character of the subjects of cancer of the lip is again emphasized by Table II.[4] The table illustrates in the first two columns the distribution throughout the counties of England and Wales of cases of death from cancer of the lip and tongue during the years 1908 and 1909. The third column sets forth the ratio of the number of deaths from cancer of the tongue to those of the lip in the corresponding county. The fourth column shows the density of population expressed as the number of persons per acre in the

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ill adapted to prove a point implying accurate observation and good memory on the patient's part and is only likely to bring discredit on clinical methods.

The small experience of the writer has yielded fairly frequent examples of association between *tuberculosis* and cancer, though an antagonism between these conditions has been suggested by some authors (e.g. Rokitansky, Lubarsch, and W. R. Williams). Thus of 141 consecutive autopsies on cancerous patients in whom the growth was elsewhere than in the mouth, coarse tuberculous lesions were revealed in 12 instances, and of 32 cases of oral carcinoma such lesions were found in 6.

[4] The data for the first two columns of this table have been obtained from records at Somerset House, unpublished and at present available only for the years 1908 and 1909. They comprise cases specified as 'cancer' of the tongue and lip, which form the great majority, a smaller group returned indefinitely as 'malignant disease' of the tongue and lip, and a very insignificant minority diagnosed as 'sarcoma' of those organs. The fourth column has been calculated from the recently published preliminary report for the census for the year 1911, while the fifth column has been estimated for 1911 on actuarial assumptions derived from the returns for the previous census.

TABLE II.

	Number of deaths from Cancer of Lip, 1908 and 1909.	Number of deaths from Cancer of Tongue, 1908 and 1909.	Ratio number of deaths from Cancer of Tongue to number of deaths from Cancer of Lip.	Density of Population in 1911 expressed as number of inhabitants per acre.	Percentage of Urban Population based on the 1911 Census.
England and Wales . .	477	1787	3·75	0·97	78
London . .	21	386	18·38	60·45	100
Surrey . .	10	49	4·90	1·98	76
Kent . . .	17	58	3·41	1·05	70
Sussex . . .	22	31	1·41	0·71	67
Hampshire .	13	42	3·23	0·87	72
Berkshire .	5	12	2·40	0·53	48
Middlesex .	8	43	5·38	6·41	95
Hertford . .	8	15	1·87	0·64	55
Buckingham.	6	9	1·50	0·48	40
Oxford. . .	8	4	0·50	0·40	50
Northampton	4	13	3·25	0·57	62
Huntingdon .	1	0	—	0·23	39
Bedford . .	3	10	3·33	0·64	60
Cambridge .	12	13	1·08	0·38	48
Essex . . .	22	50	2·27	1·47	81
Suffolk . .	8	15	1·87	0·41	49
Norfolk . .	17	17	1·00	0·38	48
Wiltshire. .	6	13	2·16	0·35	45
Dorset . . .	7	6	0·86	0·35	52
Devon . . .	11	35	3·18	0·43	68
Cornwall . .	8	15	1·87	0·37	44
Somerset . .	8	29	3·62	0·46	45
Gloucester .	17	28	1·65	0·94	73
Hereford . .	5	7	1·40	0·21	37
Shropshire .	5	8	1·60	0·28	41
Stafford . .	10	61	6·10	1·76	84
Worcester .	5	19	3·80	1·27	74
Warwick . .	9	52	5·77	1·64	78
Leicester . .	5	20	4·00	0·87	68
Rutland . .	1	1	1·00	0·19	17
Lincoln . .	8	20	2·50	0·33	55
Nottingham .	9	23	2·55	1·16	73
Derby . . .	5	18	3·60	0·98	62
Cheshire . .	11	40	3·64	1·46	81
Lancashire .	44	264	6·00	3·71	95
Yorkshire					
West Riding	29	130	4·48	1·74	88
East Riding	6	19	3·17	0·73	81
North Riding	9	23	2·56	0·33	70
Durham . .	13	62	4·77	1·80	70
Northumberland . . .	9	42	4·70	0·54	82
Cumberland .	6	13	2·17	0·27	62
Westmorland	0	3	—	0·13	42
Monmouth .	5	10	2·00	1·05	83
South Wales.	31	42	1·35	0·56	70
North Wales.	10	17	1·70	0·25	40

county, while the fifth column illustrates the degree to which the county is urbanized.

It will be seen that it is very roughly true that the more densely populated and more urban the county, the greater is the preponderance of deaths from cancer of the tongue over deaths from cancer of the lip, while the more sparsely populated and more rural districts present, on the other hand, a relatively larger proportion of cases of death from cancer of the lip. Thus in the highly urbanized counties of London, Middlesex, Stafford, Warwick, Leicester, and Lancashire, a larger ratio prevails of deaths from lingual cancer, while the rural counties of Oxford, Cambridge, Norfolk, Suffolk, Dorset, Hereford, and Monmouth have a larger proportion than other counties of deaths from labial growths. Mining areas, as Durham and Monmouth and North and South Wales, as might be expected, seem to fall under neither heading.

It is well, however, to remember that cancer of the lip is a condition more operable than cancer of the tongue, and is therefore better treated in towns, where hospitals are numerous, than in rural districts. The much happier results of operations on the lip may thus in part account for the relative scarcity of deaths in towns from growths of that region. That there is a real excess of countrymen among these cases, however, is strongly suggested by the analysis of the *occupations* of those who died from that disease (Table I).

It has been shown above that in the general death statistics, a considerable percentage of the cases of cancer of the tongue is among men with occupations in which a selection is made of the strongest and most robust. Is there any evidence of the converse of this, i. e. can a higher death-rate from this disease be proved among men following these callings than among the general population? The groups which may be selected for such an investigation are especially soldiers, sailors, and police. It is to be remembered, however, that men following the first two of these professions must be regarded as in a high degree syphilized.

At present evidence has only been obtained for the first of these groups. The death registers referring to the Chelsea Hospital for old soldiers from the year 1837 to the present day have been examined, and among 4,719 deaths of pensioners of the age of 55 and upwards, at least 62 were certified as due to oral cancer, and of these 62 at least 28 were carcinomata of the tongue or floor of the mouth, giving the proportion of deaths due to these two last causes as 6 per 1,000.

An examination of the blue books issued by the General Register Office shows that of the deaths of males over 55 years of age registered in England and Wales during the years 1901-9, only 3·5 per 1,000 deaths were due to cancer of the tongue or mouth. Thus, even with the imperfect certification and greater statistical rarity of carcinoma in earlier years,[5] cancer of the tongue

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[5] The tendency of the death-rate from carcinoma linguae to statistical increase in England and Wales is illustrated and dealt with in the 72nd Annual Report of the Registrar-General, p. xci.

appears to have been nearly twice as common among this group of old soldiers as among the general population of comparable age in Britain to-day.

III. *Analysis of the Age Factor in Oral Carcinoma.*

The average age of onset of 250 hospital cases of oral carcinoma was 56·2 years.

Under the heading 'Oral Carcinoma' are included cases of carcinoma of the tongue, floor of the mouth, inner side of the cheek, tonsil, palate, and lip, but, except in the case of the labial form, such clinical differences as these groups represent did not seem sufficient to justify separation into clinical entities. Thus it is not unusual to meet a condition of leucoplakia of the inner side of cheek or palate with a developed epithelioma of the tongue or floor of the mouth, and, on the other hand, a condition of leucoplakia of the tongue is a not uncommon accompaniment of a growth of malignant nature on cheek, palate, or tonsil. Again, it is easy to speak of an epithelioma of the floor of the mouth and to distinguish it from an epithelioma of the tongue, but clinically a growth may appear in the angle between tongue and floor of mouth, so that it is impossible to say to which of the two organs it should be ascribed.

Carcinoma of the lip, on the other hand, seems to be better differentiated from the generality of oral cancer, and patients with this disease present certain aetiological characters that may justify its separation from the larger group of oral malignant growths to which it might otherwise have been expected to be closely assimilated.

With most diseases apt to declare themselves in the declining years of life, the frequency of incidence usually increases up to a certain age and then rapidly diminishes, the decrease being conditioned by the smaller numbers of the population surviving to the more advanced years. If, however, instead of the actual numbers of cases occurring at different ages, the relative incidence *per million living* within the various age periods be considered, the liability to the disease at the various periods of life is disclosed, and points illustrating the natural history and aetiology of the morbid condition may become apparent.

For the purpose of an inquiry into the relative *rate* of incidence, or of death, at different ages from oral cancer, hospital statistics are peculiarly unsuited. The patients from whom such statistics are derived are drawn only from certain social strata; persons at the extremes of life are often unwilling to enter these institutions, and, moreover, the type of case admitted is usually determined by a standard of operability.

Cancer of the tongue is a rapidly and almost uniformly fatal disease, and, in the writer's opinion, the investigation of the relative death-rate from this and allied conditions, at different ages and in the two sexes, may be reliably made by the light of the statistics obtained from the death records of the Registrar-General. It is sometimes urged against the use of these data for cancer investigation, (1) that many of the cases are not accurately diagnosed, and, especially, that the

microscope is not in constant use as for hospital cases—that, in fact, there is a great variation in the accuracy, care, and skill with which medical men make their certifications—and (2) that many doctors are reluctant for social reasons to record a statement that the patient was the subject of cancer. Against the first of these objections it may be maintained that the vast majority of cases of oral cancer, in the advanced state when death ensues, are almost unmistakable, and that, especially when the site of the growth is the tongue or lip, diagnosis can hardly be rendered more certain by microscopic examination. The second objection is met by the consideration that however the medical attendant may hesitate to diagnose cancer on the death certificate, there is no reason why this reluctance should act with especial force with regard to any material age period. The error, if any, is therefore uniformly distributed in a large series of cases.

The analyses of death-rates due to oral carcinoma are based on deaths that took place between the years 1901 and 1909 inclusive, and in the following charts are represented in curves with a continuous line for the male and a broken line for the female sex. An attempt has been made throughout to adjust all curves to a comparable size, as the point to be brought out is not the actual frequency of deaths from the causes involved but their *relative frequency at different age periods* and in the two sexes.

The returns of deaths from oral cancer are classified by the Registrar-General under the headings: Tongue, mouth, lip, jaw, pharynx and throat, larynx and trachea. Of these, cancer of the tongue is perhaps the easiest of diagnosis, and (at any rate in the advanced states in which death results) the least likely to be confused with any non-cancerous condition. It is, moreover, a comparatively common disease and may be taken as the type of oral carcinoma.

The death-rate presented by cancer of the tongue has certain peculiarities which are not shared by that of cancer of other parts of the body. It differs in the first place from the death-rate from malignant disease of those other parts of the body in which a liability is shared by both sexes, in the marked difference in character of the age incidence of males and of females (Chart I). The death-rate from cancer of the tongue in males rises steadily until about the sixty-fifth year, when the rate remains almost uniform for two decades, to fall again in extreme old age. In the female cases the death-rate rises slowly at first and by no means parallel to the male; then, becoming accelerated about the sixtieth year, it rises rapidly to a maximum at or about the eightieth year, and again falls slightly (though less than the male curve) at the extreme limit of life.

The chart illustrating the death-rate from lingual cancer thus presents the following characteristic features: (*a*) The dissimilarity of the male and female curves; (*b*) the approximately equal rate for males in the decades 65–75 and 75–85; (*c*) the drop in extreme old age in both sexes. As regards the general form of the curves presented by this group of cases, it may be said that while the male curve is a type of its own, the female curve accords fairly well

with those for cancer of several other parts of the body and is, for example, closely similar to the curve for the rectum of either sex (Chart VIII).

Turning now to cancer of the lip (Chart III), we meet with an altogether different form of curve. Here not only is there a close similarity throughout for the two sexes, but the curve of either sex is still accelerating its rate of rise at the last extreme of life for which we have records. Here also analogies can be drawn from cancerous disease of other parts, for the curve derived from cancer of the lip is closely similar in type to the curves derived from such conditions as cancer of the breast (Chart IX) or of the skin of the face (Chart X).

The next group to be considered has been inadequately notified as 'Malignant disease of the Mouth', and doubtless comprises a number of heterogeneous conditions. The commonest malignant growths of the mouth, however, are cancer of the tongue and cancer of the lip. It is therefore significant to find that the curve representing the death-rate from conditions certified as 'Malignant disease of the Mouth' (Chart II) is, in males, of a form intermediate between that of malignant disease of the tongue and malignant disease of the lip. Thus, while it presents the horizontal portion between the seventieth and eightieth years of life found in the former, it has also the upward tendency in extreme old age characteristic of the latter. With regard to deaths of females notified as due to 'Malignant disease of the Mouth', the curve of death-rate is closely parallel to that of the male death-rate from the same cause and has also, curiously enough, the horizontal portion which was found for cancer of the tongue in males, but which was not present in the death-rate curve of females from that cause.

The rate curve for 'Cancer of the Jaw' in females (Chart IV) is practically identical with that for cancer of the tongue in the same sex, though the male curve for cancer of the jaw resembles less definitely the male curve for the tongue and has not its characteristic flat top. Similar curves to that for 'Cancer of the Jaw' are yielded by the death-rates from cancer of the rectum (Chart VIII) and of other parts of the body.

There yet remain the groups of cases of deaths certified as due to cancer of parts described as pharynx and throat, and larynx and trachea.

From a clinical point of view these headings are likely to include a number of diverse pathological conditions, some of them perhaps not being really cancer. It seems improbable that much result will accrue from a scrutiny of so incongruous a series of cases, and a glance at Charts V and VI will convince the reader of the conglomerate character and mutual incomparability of the death-rates from these sources.

The group classed by the Registrar-General under 'Deaths from Malignant disease of the Oesophagus' doubtless also includes a considerable number of cases which are not cancer at all; and the condition, though comparatively easy to diagnose clinically, especially in its later stages, must yet be classed among the inaccessible or only partially accessible sites, the statistics for which cannot

be considered reliable.   Clinically the aetiological factors of this condition are very obscure, though pathologically they fall in line with the new growths in the tongue.   As in the case of the tongue, also, it is not infrequent to find post-mortem leucoplakic patches in the non-ulcerated portions of an organ that is the seat of a carcinoma.   The rate curves for this condition (Chart VII) resemble those for carcinoma of the tongue in the existence of a fall in both sexes towards the extreme of life, while the maximum rate is later in the case of females than in the case of males.   As in the lingual group, the female curve differs from the male, but unlike that group there is no horizontal portion to the male curve.

It will thus be seen that three main types of death-rate curves have been considered :—

(a) Curves illustrated by cancer of the lip, of the breast, and of the skin, in which the death-rate rises progressively from youth to extreme old age ; the curve is similar for the two sexes.
(b) Curves illustrated by cancer of the rectum and of other parts of the body, in which there is a progressive rise commencing in early middle life, becoming less marked and finally falling in advanced life ; the curve is similar for the two sexes.
(c) Curves illustrated by cancer of the tongue, which differ in the two sexes. In the male there is a steady but not accelerated rise in middle life.   There then follows a more or less plateau-like summit and in late life a slight fall.   The curve in the female accords with type (b), there being a progressive rise succeeded by a slight fall in advanced years.

It has moreover been suggested that cancer arising in parts of the oral mucous membrane other than that of the lip may be regarded as according in a general way with male type (c), but more or less concealed and modified by elements of (a) and (b).

IV.   Syphilis and Oral Cancer.

(See Appendices A and B.)

There can be no doubt of an intimate association between antecedent syphilis, leucoplakia, and the development of oral carcinoma.   Cancer of the tongue, however, is preceded by a definite leucoplakia in only a proportion of cases, while many subjects of cancer of the tongue and other parts of the mouth have a history of syphilis but no clinical signs of leucoplakia.   It is also not uncommon in cases of carcinoma linguae to meet with a condition in which there is a general tendency to smoothness and thinness of the mucous membrane of the tongue without any specially thickened or corneous areas, but presenting a reduction in number and size of the papillae down to a complete disappearance of these structures.   It is noteworthy, also, that while lingual warts and corns are a common accompaniment of cancer of the tongue, the development of the new growth at the actual site of one of these thickenings has not been shown to be the general rule.

Some observers have remarked that the syphilis antecedent to oral cancer

has often been of a severe or malignant type, and it is not infrequent in such cases to meet with tertiary rashes. The nervous system seldom seems to bear the brunt of the antecedent syphilis, and the writer has noted only one case that combined tabes dorsalis with carcinoma linguae (Appendix A, Case 5). This dissociation may perhaps be partly explained on the ground that locomotor ataxy occurs as a rule within ten years of infection, and therefore most commonly between the ages of 30 and 40, so that tabetics have frequently succumbed before they reach the cancer age.

The degree of association of syphilis and cancer in the author's cases is illustrated in the following table :—

TABLE III.

Syphilis and Oral Cancer.

Site of Primary Growth.	Number of cases investigated.		Number of cases found to be syphilitic.	
	Males.	Females.	Males.	Females.
Tongue	60	1	34 (10 doubtful)	1 (1 doubtful)
Floor of mouth	6	0	3 (1 doubtful)	0
Inner side of cheek	2	0	2	0
Tonsil	2	1	1	1 (1 doubtful)
Lower jaw	1	0	0	0
Palate	2	0	1 (1 doubtful)	0
Upper jaw	1	2	0	0
Lip	14	1	6	1 (1 doubtful)
	88	5	47 (12 doubtful)	3 (3 doubtful)
	93		50	

Syphilis and Non-Oral Cancer.

Site of Primary Growth.	Number of cases investigated.		Number of cases found to be syphilitic.	
	Males.	Females.	Males.	Females.
Glands of neck	6	2	3	0
Oesophagus	19	0	2 (1 doubtful)	0
Stomach	15	11	0	0
Large intestine and rectum	47	37	5	0
Skin	30	8	4 (1 doubtful)	0
Cervix uteri	—	100	—	5 (3 doubtful)
Corpus uteri	—	9	—	0
Breast	1	132	—	3 (2 doubtful)
Other parts	11	8	1	0
	129	307	15 (2 doubtful)	8 (5 doubtful)
	436		23	

Thus, in a series of 93 consecutive cases of oral cancer, a history of syphilis was obtained in 50 (15 of them more or less doubtful), making (between 38 and) 54 per cent., a proportion not greatly lower than is sometimes obtainable from the history sheets of tabetics or of general paralytics. The proportion of cases of oral carcinoma in which the writer has traced a syphilitic history is perhaps rather higher than has been found by many observers and is only slightly below that met with in the subjects of thoracic aneurysms.

On the other hand, in 436 cases of cancer of parts other than the mouth, syphilis had been a preceding condition in only 23 (7 doubtful), making a percentage of (between 4 and) 6.   Of the non-oral cases 307 were females, and evidence of syphilis was only obtained in 8 of these, (of which 5 were doubtful, and) 2 were cases of the congenital disease who had developed carcinoma of the cervix uteri.   Of the 23 subjects of non-oral cancer associated with syphilis, only 9 cases were glandular, leaving 14 of the squamous variety.   If to these be added the 50 cases of oral cancer in which the association of syphilis was present and which were all of squamous type, it will be seen that among a series of 73 cases of association of syphilis and cancer 64 were squamous and only 9 glandular.   It is also possible that squamous-celled carcinoma of the cervix uteri is more frequently associated with crypto-syphilis than is made apparent by these results, for a large percentage of such cases give a history of mis-carriages, more or less numerous.

One fact stands out well from these figures, viz. that syphilis is far more frequently associated with most forms of oral cancer than with malignant growths of other regions.

Wassermann's reaction for the deviation of the complement, when applied to cases of carcinoma linguae, yields interesting results, but no very definite conclusions can be drawn from the data available except, again, the greater frequency of a syphilitic history in this than in other types of cancer.

An investigation of the reaction has been undertaken by Dr. Foerster in the laboratories of the Cancer Hospital, and his results on cancer and allied conditions are here summarized:—

Twelve cases of cancer of the tongue and of the floor of the mouth were examined, eight of them giving a history of syphilis.   In three instances the reaction was positive, and two of these three admitted infection while the third denied it.

Three cases of leucoplakia (one of whom denied syphilis), two cases of glossitis (one of whom denied syphilis), and one case of lingual mucous plaques all gave a positive Wassermann reaction.

Twenty-five cases of non-oral carcinoma of various parts of the body were investigated, and Wassermann's reaction was obtained in only two, though several others gave a history of syphilis.   One of these two cases was a rodent ulcer, and the other on further examination yielded evidence that the growth may have been of oral origin.   He was a man aged 45, admitted for a huge bilateral swelling of his neck of some years' duration.   He strenuously denied all possibility of syphilitic infection and there was nothing in his history to suggest it.   His blood was examined many times and always yielded a positive reaction.   The growth was a squamous-celled carcinoma, and at autopsy the right tonsil was found to be involved, and it then appeared possible that this may have been the primary seat of the cancer.   A well-marked aortitis was present (Appendix B, Case 1).

The general physical and cardiovascular conditions of a number of cases of carcinoma associated with syphilis may be gathered from Appendix A (Oral) and Appendix B (Non-oral).

V. *Podagra and Oral Cancer.*

(See Appendices A and C.)

The relationship of 'arthritism' and cancer has been emphasized by French observers. It must, however, be borne in mind that at the period of life when carcinomatous growths most often develop, rheumatoid changes are a common phenomenon.

The writer has frequently observed the coexistence in the same patient of cancer with rheumatoid arthritis and with various forms of osteoarthritis. He has, however, failed to obtain evidence of a more frequent association between these conditions than may be explained by their similar age incidence. The arthritic state has usually been moderate in degree, and in only two or three instances could the patient be regarded as crippled by the progress of the arthritis.

A history of rheumatic fever is not uncommon among carcinomatous patients of the hospital class, but it is also frequent in patients of the same class who are not subjects of malignant growth, and the writer has not succeeded in obtaining evidence that rheumatism is commoner in one group than in the other. Cardiac disease, it is true, has been frequently found in association with cancer, but the condition of the heart has in most cases been of degenerative origin rather than of the type met with as a sequel to rheumatic infection (see Section VI).

As regards gouty affections, however, the position appears to be different. Cancerous patients as a class have *not* indeed been frequently found to be the subjects of gout, hardly perhaps more often than might be expected from a consideration of the ages at which malignant new growths are most apt to declare themselves. An exception must, however, be made for the group of carcinomata of oral, and to a partial extent for those of rectal and of epidermal origin. The results of the investigation are summarized in the following table :—

TABLE IV.

Gout and Oral Cancer.

Site of Primary Growth.	Number of cases investigated.		Number of cases found to be gouty.	
	Males.	Females.	Males.	Females.
Tongue	60	1	18	0
Floor of mouth	6	0	0	0
Inner side of cheek	2	0	1	0
Tonsil	2	1	0	0
Lower jaw	1	0	0	0
Palate	2	0	0	0
Upper jaw	1	2	0	0
Lip	14	1	2	0
	88	5	21	0
	93		21	

TABLE IV (*continued*).

Gout and Non-oral Cancer.

Site of Primary Growth.	Number of cases investigated.		Number of cases found to be gouty.	
	Males.	Females.	Males.	Females.
Glands of neck . . .	6	2	1	0
Oesophagus	19	0	1	0
Stomach	15	11	0	0
Large intestine and rectum	47	37	5 (2 doubtful)	0
Skin	30	8	6 (1 doubtful)	0
Cervix uteri . . .	—	100	—	0
Corpus uteri . . .	—	9	—	0
Breast	1	132	0	2
Other parts	11	8	0	0
	129	307	13 (3 doubtful)	2
		436		15

In some cases the history of gout was obscure, and in a malady so protean the details of past history will naturally not always be so definite as to satisfy every observer. Such instances have been excluded altogether from the oral cases, and in the other groups have been marked as doubtful. In a considerable percentage of the cases, however, definite evidence of a gouty tendency has been secured and clear histories of gouty attacks have been obtained, and some, indeed, presented marked lesions characteristic of the disease. In many the writer has himself been able to witness acute attacks, and for others he has secured accounts of such attacks from medical men who had opportunities of witnessing them.

Out of 93 consecutive cases of cancer of the oral region, gout had been an antecedent in 21, making 23 per cent. On the other hand, in 436 cases of cancer of parts other than the mouth, gout had been a preceding condition in only 15 (3 doubtful), making a percentage of (between 3 and) 4. Of the non-oral cases 307 were females and evidence of gout was obtained in but 2 of these. If male cases only be considered, gouty manifestations were found to be about twice as common in oral as in non-oral cases. Of the 36 cases of the association of podagra and cancer that have been observed, the growth was squamous-celled in 29 and glandular in 7.

Gout in association with cancer in females was noted in only two cases. In one of these, however, it was in a very severe form. A woman, aged 70, had for some years been treated together with her sister for severe intractable hereditary tophaceous gout. During an examination of the chest a lump was accidentally discovered in the breast which on excision proved to be typical scirrhus carcinoma (Appendix C, Case 14).

A short history of oral cases with associated podagra is incorporated in Appendix A, while the few non-oral podagrous cases will be found in Appendix C.

VI. *Cardiovascular Conditions in Oral Carcinoma.*

The general physical conditions associated with oral carcinoma are of such a character that a high degree of arterial degeneration may be expected in its victims.   In a group of people at least 82 per cent. of whom are males, and 69 per cent. over 55 years of age, of whom some 54 per cent. have suffered with syphilis and perhaps 23 per cent. with gout, who are, moreover, in the main, persons largely built, of plethoric disposition and often emphysematous— among such a population a high degree of arterial degeneration may well be expected.

A study has been made of the cardiovascular conditions of a series of these patients, both clinically and post mortem, and at least as high a degree of degeneration as was foreseen has been found.   Whether or no there is *more* cardiovascular change than is explained by the antecedent factors of oral cancer can only be determined after a more extensive and detailed analysis of the data, and a definite conclusion may need to be deferred until there is a fuller know- ledge of the nature, origin, and distribution of vascular degeneration in general. Very tentatively, however, the writer ventures an opinion that there *is* a greater degree of vascular degeneration in the subjects of oral cancer than is explained by the known factors of that condition, and that arteriosclerosis and other vascular changes occur to an unexpected extent even in comparatively young subjects, in women and in cases which have suffered with neither syphilis nor gout.   This view is supported by the renal conditions associated with carcinoma, but it is evident that the matter needs considerable further attention.

A great difficulty in estimating the degree of vascular degeneration is the apparent arbitrariness of the distribution of these changes.   In many subjects the radial arteries show the most marked thickening, though the brachials are comparatively free.   Often, again, the heart may show evidence of degenerative change while the vessels of the limbs may be like those of a young man.   Even at a post-mortem examination the difficulty is frequently hardly less, for while the ascending aorta and coronaries may be free from atheroma, the abdominal aorta may show calcification and the most advanced degenerative change, or the position may be reversed, the ascending aorta being highly degenerate and the rest of the great vessels comparatively free from morbid change.

At the time of writing the author has under observation two elderly men, both the subjects of cancer now and of syphilis thirty years ago.   Both of them have been soldiers, both exhibit well-marked gouty manifestations, and one has till recently worked as a painter.   And yet, with these factors of vascular degeneration, the peripheral vessels of both patients are, so far as can be clinically ascertained, as soft and pliable as those of healthy young men who have never misused their powers, and in both (though one is 68 years of age) the heart seems fairly healthy.   But no real index of the general vascular condition is yielded by this examination, for both cases are hemiplegic and have

been the subjects of cerebral haemorrhages (Appendix A, No. 51, and Appendix B, No. 23).

A general statement of the vascular condition of cancerous patients is rendered yet more difficult by the imperfect scrutiny to which the peripheral vascular system itself is usually submitted even at autopsy. In most post-mortem examinations, the heart and great vessels indeed are investigated in detail, a process that the fear of mutilation forbids for the smaller branches; and although these larger vessels give a very imperfect indication of the state of the peripheral arteries, that index is yet the only one at present available from post-mortem records.

In a series of clinical examinations, the vascular conditions of the subjects of cancer have been carefully noted. The condition of the radial artery forms as good an indication as any accessible during life of the general state of the peripheral vessels, and observations on this point and on the cardiac state are tabulated in the Appendices.

In cases of oral cancer senile forms of cardiac disease are frequently found, and the clinical signs of this condition are often demonstrable. Among the points most frequently noted are such conditions as tachycardia, dropped beats, cardiac arrhythmia, faint heart sounds, accentuated aortic second sound, cyanosis, bronchitis, and cardiac hypertrophy and dilatation (see Cardiovascular column of Appendix A). In the writer's experience, these conditions in cases of oral carcinoma have been not only commoner than in the generality of the population subjected to wear and tear, but also commoner than in the subjects of other forms of cancer.

The post-mortem material has borne out the conclusions reached by observation of the living patients. Mitral sclerosis, a common condition in elderly subjects, has been found with about equal frequency in all forms of carcinoma investigated. Aortic valvular disease, on the other hand, appears to be more than twice as frequent in the subjects of oral cancer as in those of malignant growths of other parts. The aortic valves were found to be diseased in 21 per cent. of autopsies on the subjects of oral cancer, and in many cases the valvular lesion was of an advanced degree. Atheroma of the aorta was present to a noteworthy extent in no less than 72 per cent. of the oral cases, and in some of them was extreme. One aorta was the site of a saccular aneurysm, while in five (of ninety-five cases) the arch of the aorta was definitely dilated.

In the non-oral cases, on the other hand, atheroma of the aorta had reached a noteworthy extent in but 41 per cent. and was on the whole of a lower degree, and, as might be expected from the above figures, cardiac hypertrophy was also less commonly encountered than in the oral group. The other cardiac lesions seem to be fairly uniformly distributed between the oral and the non-oral groups.

TABLE V.

Analysis of cardiovascular conditions in 366 consecutive post-mortem examinations.

		Males.	Females.
271 Non-oral cases consisting of:—			
66 cases of cancer of the breast		1	65
61 ,, ,, colon		22	39
40 ,, ,, cervix		—	40
30 ,, ,, stomach		18	12
17 ,, ,, skin		8	9
13 ,, ,, oesophagus		12	1
12 ,, ,, body of uterus		—	12
8 ,, ,, ovary		—	8
4 ,, ,, bladder		2	2
3 ,, ,, glands of neck		3	0
4 ,, ,, pancreas		3	1
13 ,, ,, other parts		7	6
		76	195
95 Oral cases		88	7
		164	202
		366	

		Percentage of Oral cases.	Percentage of Non-oral cases.
Pericardium	Adherent	1·1	2·2
	Fibrous plaques	8·4	2·7
Myocardium	Hypertrophy	13·7	7·0
	Brown atrophy	14·5	18·8
	Marked fibrosis	7·4	6·2
	Marked fatty change	4·2	4·8
Endocardium	Mitral sclerosis	29·5	24·0
	Aortic sclerosis	21·0	8·9
	Tricuspid sclerosis	1	1·8
Atheroma of aorta of noteworthy extent		71·6	41·3

VII. *Renal Disease and Oral Cancer.*

The renal conditions in cases of carcinoma submitted to post-mortem examination appeared to be closely parallel to the cardiovascular conditions.

The proportion of the population between 50 and 60 years of age with granular kidney has been placed as high as 43 per cent.,[6] and on this basis the percentage among cases of non-oral carcinoma is about that of the rest of the population.   But in the oral group even the high percentage thus suggested is considerably exceeded, though a comparison of renal conditions in oral and non-oral cancer is made difficult by the fact that hydronephrosis and its accompanying renal disorganization were present in 20 per cent. of the rectal and in 55 per cent. of the uterine cases.

For the purpose of this investigation the cases of interstitial nephritis were divided into slight, moderate, and advanced, and the following results were obtained :—

[6] By Mahomed, quoted by S. West, Lettsomian Lecture, 1900.

TABLE VI.

Chronic interstitial Nephritis.	Oral Cancer 95 cases Percentage.	Non-oral Cancer 271 cases Percentage.
Slight	16·9	15·6
Moderate	22·1	10·4
Advanced	14·7	6·7
	53·7	32·7

The high percentage and degree of renal change encountered in oral cancer may be perhaps in part explained by the extensive and profound septic element in these cases, but in most cases microscopic examination has shown the interstitial change to be patchy and more marked towards the cortex, suggesting a general vascular rather than a simple toxic origin. The average weight of the kidneys was distinctly subnormal, but as most of the bodies were highly emaciated on reaching autopsy, no conclusion can justly be drawn from this observation.

VIII. *Emphysema and Oral Cancer.*

Large-lunged emphysema is a disease often found in the subjects of arterial degeneration and is so common at the cancerous ages that it may reasonably be expected with considerable frequency in bodies dead of malignant growth. The emphysema associated with cancer has been found to be usually moderate in degree and widely diffused throughout the lungs, being more marked microscopically than macroscopically. Large bullae with well-marked pulmonary enlargement have been infrequent features.

Clinically, it has been noted in many cases that the chest tended to be barrel-shaped and its movements poor, that the audible air entry was slight, that a tendency to bronchitis was frequent, and that the cardiac dullness was often difficult to ascertain. These facts were borne out by post-mortem examination with microscopic investigation. Little difference, however, was found in the distribution of this pulmonary condition in oral and in non-oral carcinoma, for while emphysema was observed in 47·4 per cent. of 95 consecutive post-mortems of oral cancer, it was present to a noteworthy degree in 40·2 per cent. of 271 consecutive autopsies of bodies with growths of parts other than the mouth.

IX. *Points in the Aetiology of certain Cardiovascular Diseases compared with Oral Cancer.*

The aetiology of thoracic aneurysm clearly presents certain general parallels to that of carcinoma of the tongue. In about 66 per cent. of cases aneurysm has been ascertained to be of syphilitic origin ; it is much commoner in men than in women, and its maximum incidence is at a somewhat similar age to that of cancer of the tongue. Moreover aneurysm is especially liable to occur in big strong men who are likely to be subjected to sudden strains, and is a condition

naturally associated with various forms of arterial degeneration, aortic disease, and valvular lesions. Under these circumstances, it is not a matter for great surprise that the death-rate curves for aneurysm present certain similarities to those of lingual cancer.

Aneurysm, like tongue cancer, proves fatal in the great majority of cases, and though mortal results may be somewhat longer deferred, yet here also the death-rate must approximate to the rate of liability to the disease. Again, as in the case of lingual cancer, diagnosis in early stages of the disease presents certain difficulties, but these usually disappear as the condition advances, and in the last stages the state of affairs is generally patent enough.

The death-rate curve of aneurysm presents the following points of similarity to that of cancer of the tongue (compare Chart XII and Chart I) :—

(*a*) The curves for the two sexes differ markedly from one another, and in a fashion similar to those of lingual cancer.

(*b*) In the male curve, as in that for lingual cancer, there is an early and abrupt rise, the convexity of which is upward, becoming less steep until a portion is reached which approaches the horizontal, and finally the curve falls in old age.

(*c*) In the female curve, as in lingual cancer, there is a less sudden rise in earlier years, becoming steeper so that the curve presents an upward concavity. After reaching a maximum there is an abrupt drop in old age.

The curves obtained from the death-rate due to aneurysm and that due to cancer of the tongue present, however, certain differences to which attention may be drawn :—

(*a*) The horizontal portion of the curve of aneurysm occurs at an earlier age than that of lingual cancer. Syphilis and strain seem to have done their worst in causing arterial disintegration *before* the age of onset of the maximum death-rate from lingual cancer.

(*b*) The decline in old age in the death-rate from aneurysm in females is much more rapid than in males. Strain is so large a factor in the aetiology of aneurysm that the period of life at which females especially are usually relieved of this cause of the disease is naturally one in which the death-rate rapidly declines.

Among the commonest causes of death in elderly people of both sexes is to be reckoned *cerebral haemorrhage*. Like aneurysm, this condition is associated with vascular degeneration, but, unlike aneurysm, no overwhelming factor in its aetiology is contributed by syphilis, and although ' strain ' is frequently given as a cause, clinical experience shows that the strain is perhaps most often of so slight a nature as to come within the everyday experience of people living normal lives.

In the reports of the Registrar-General since 1901, cases of deaths from cerebral haemorrhage are classed under two headings : (1) Cerebral Haemorrhage and Cerebral Embolism ; (2) Apoplexy and Hemiplegia.

The inclusion of cerebral embolism in the group of cerebral haemorrhage does not greatly disturb the results, as it is comparatively rare, and especially so at material ages. In the curves in Chart XIII, the two groups have been added

together and the death-rate from them calculated, but almost identical curves could have been presented from either group by itself.

The curves for cases of haemorrhage of cerebral origin for the two sexes are very much alike, and for a part of their course are indeed practically coincident. Rising at first slowly, these curves become more steep and are still rapidly rising at the highest ages for which statistics are available, and show no tendency to return to the base line at any part of their course.

These curves obtained from death-rates from cerebral haemorrhage are closely similar in form and character to such curves as those for cancer of the lip (Chart III), cancer of the breast (Chart IX), or cancer of the skin of the face (Chart X). In a death-rate curve that rises throughout its course we may suppose that we have to do with some element or elements acting *throughout* life and with cumulative force as age advances. This factor in the case of cerebral haemorrhage we associate especially with arterial change, the result of the normal wear and tear of life; and it may well be that some factor acting *throughout* life and accumulating with the years will be found to be a determinant in those cancerous growths whose rate curves accord with this type.

In the case of cancer of the lip it is commonly held that small and repeated traumatic lesions such as may be caused by the stem of a tobacco pipe form such a factor, and clinically it has been found that a history of irritation of this kind is obtainable more frequently in cases of cancer of the lip than in cases of cancer of the tongue.

Evidence of vascular changes in labial carcinoma obtained from post-mortem sources is necessarily limited, for there seem to be few deaths from this disease in the great towns (thus in 1909 there were only seven deaths recorded as due to ' Malignant disease of the Lip' in London). In the analogous case of breast cancer, however, with its continuous and accelerated death-rate curves, no marked cardiovascular element has been distinguished.

In the curve represented in Chart XII, on the other hand, we must consider that we have to do with factors that act at certain periods of life with special intensity and from which those who survive those periods are comparatively free or at least have acquired some immunity. Among these factors in the case of aneurysm, syphilis and strain are well recognized, and on the same lines the writer would point to syphilis, gout, and 'plethora' as factors in the development of oral cancer.

These factors in the case of cancer of the tongue, like the parallel factors in the production of aneurysm, act very differently in the two sexes and produce curves of different types. There is an analogy, perhaps, in the curves for the two diseases which may be more than accidental.

X. *Conclusions.*

The following provisional conclusions may be very tentatively enunciated :—

1. It is thought that carcinoma beginning in the oral mucous membrane may form a separate clinical entity, in which carcinoma of the oesophagus should

perhaps be included, but from which epithelioma of the lip should probably be excluded.

2. The cases forming this oral group of cancer do not, as a class, form an average sample of the general population. They appear to differ from the general population in the following particulars:—

(a) There is an overwhelming preponderance of males over females among them.

(b) A large percentage have suffered from syphilis, often of very severe type.

(c) Many are stout, heavy, plethoric men, of the type well illustrated in actual life by our police and soldiers. They are most often men of exceptionally robust previous health. These facts are emphasized by their social position and occupations.

(d) That their metabolism is probably not that of the normal population is suggested by the fact that a considerable percentage of them have suffered more or less severely with gout, usually of a typical and easily recognizable form.

(e) Although apparently healthy except as regards the local disease and the effects of syphilis and gout, these patients exhibit evidence of renal interstitial change and arterial degeneration. It is true that vascular and renal degenerative changes are apt to declare themselves at a period of life when carcinoma of the mouth is most common. Yet even allowing for this, and allowing for syphilis and gout as antecedent conditions, there still appears to be a further unexplained predominance of vascular and renal change among cases of oral cancer.

3. The liability to oral carcinoma at various ages differs from that of cancer of other regions in a special manner; this difference may be graphically expressed in death-rate curves which are characteristic of this malady and are typified by the curves for cancer of the tongue.

It is suggested that these peculiarities may be in part explained by assuming that the earlier cases are more frequently of syphilitic origin, while the later have other associations, among which gout is to be reckoned.

4. Aneurysm and certain vascular diseases present certain analogies to some types of oral carcinoma, especially as regards age distribution, and it seems not unlikely that these analogies may be related to similar aetiological factors.

CHART I

Rate per million living

Death rate from
Cancer of Tongue
in England and
Wales 1901-1909

Males ————
Females --------

CHART II

Rate per million living

Death rate from
Cancer of Mouth
in England and
Wales 1901-1909

Males ————
Females --------

CHART III

Rate per million living

Death rate from
Cancer of Lip
in England and
Wales 1901-1909
Males _____
Females - - - - - - -

CHART IV

Rate per million living

Death rate from
Cancer of Jaw
in England and
Wales 1901-1909
Males _____
Females - - - - - - -

CHART V

Rate per million living

Female	Male
40	160
30	120
20	80
10	40

Death rate from
Cancer of Pharynx
and Throat in England
and Wales 1901-1909

Males ——————
Females - - - - - - - -

Years
25   35   45   55   65   75   85

CHART VI

Rate per million living

Female	Male
30	120
25	100
20	80
15	60
10	40
5	20

Death rate from
Cancer of Larynx
and Trachea in
England and Wales
1901-1909

Males ——————
Females - - - - - - - -

Years
25   35   45   55   65   75   85

CHART VIII

Rate per million living

Death rate from Cancer of the Rectum in England and Wales 1901-1909

Males ——— Females ------

CHART VII

Rate per million living

Death rate from Cancer of the Oesophagus in England and Wales 1901-1909

Males ——— Females ------

CHART IX

CHART X

CHART XI

Rate per million living

Death rate from
Cancer of Uterus
in England and
Wales 1901-1909

CHART XII

Rate per million living

Death rate from
Aneurysm in
England & Wales
1901-1909
Males ————
Females --------

CHART XIII

APPENDIX A.

93 *Cases of Oral Carcinoma.*

Case 1. Male, aged 66. **Part affected** : Tongue. **Duration** : $2\frac{3}{12}$ years. **Physical condition** : Very strong muscular man ; has been a professional cricketer. **Cardiovascular condition** : Artery at wrist and in upper arm very hard and tortuous. P. M. Definite dilatation of aorta. A good deal of atheroma of aorta. Kidneys healthy. **Gout** : On several occasions has had attacks of swelling and pain in the feet, chiefly in the dorsal part, and sufficiently severe to lay him up. These attacks usually start in the big toe. Tophi in ears. P. M. Well-marked chronic changes with lipping in the metatarso phalangeal articulations.

Case 2. Male, aged 53. **Part affected** : Tongue. **Duration** : 2 years. **Physical condition** : Rather small man. Has had very good health. **Cardiovascular condition** : High tension pulse. Artery wall at wrist is much thickened. P. M. Mitral valve thickened. Definite dilatation of ascending aorta but no atheroma. 'Arteriosclerotic' kidney with little microscopic change.

Case 3. Male, aged 75. **Part affected** : Tongue. **Duration** : $\frac{1}{12}$ (?) year. **Physical condition** : Very sturdily built old man. Has had very good health and 'never had a day's illness '. **Cardiovascular condition** : Artery wall at wrist much thickened and very hard. A systolic murmur at aortic area traceable into neck. Murmur can be heard all over the praecordium. P. M. Fibrosis of mitral valves. Large vessels healthy. Lungs emphysematous and fibrosed. Kidneys fairly healthy. Adenoma in right kidney. **Syphilis** more than fifty years ago. Wife has had six pregnancies, five of which terminated in miscarriages. **Remarks** : Wife had breast removed for cancer twenty years ago. Tongue and pharynx in Museum of Cancer Hospital, New Series, No. 566 ; kidney, No. 544.

Case 4. Male, aged 51. **Part affected** : Tongue. **Physical condition** : Well-nourished muscular man. Very good health. **Cardiovascular condition** : Artery wall at wrist somewhat thickened.

Case 5. Male, aged 53. **Part affected:** Tongue. **Physical condition:** Well-nourished muscular man. **Cardiovascular condition:** Radial arteries not thickened. Healthy heart. Syphilis thirty years ago and treated only for two months. He had a very bad rash which has left much scarring. There is now a well-marked tertiary syphilide. Knee-jerks greatly diminished and some Rombergism. Has been married many years, but wife has never become pregnant.

Case 6. Male, aged 61. **Part affected:** Tongue. **Duration:** $\frac{1}{12}$(?) year. **Physical condition:** Strong, healthy, heavily built man. **Cardiovascular condition:** Radial artery much thickened. P.M. Heart fairly good. Patchy atheroma of aorta, increasing peripherally and well marked at bifurcation. Kidneys small and firm. Microscopically moderate diffuse fibrosis.

Case 7. Male, aged 55. **Part affected:** Tongue. **Duration:** $\frac{6}{12}$ year. **Physical condition:** Very fine physique. Has been a soldier, reaching rank of sergeant, and employed afterwards at War Office. **Cardiovascular condition:** Radial artery large and pulse full. All arteries seem dilated and their walls thickened. No cardiac murmurs. P.M. Mitral and aortic valves thickened and calcareous. Ascending aorta dilated and contains many calcareous plaques, erosions, and scars. Kidneys granular with adherent capsule and diminished cortex. Syphilis twenty-five years ago with primary sore and secondary rash. Treated by military surgeons for two years. Two years after infection had abscesses all over body. He suffered with mucous plaques round anus. P.M. was found a definite syphiloma of testicle. Patient has never had any living children. His wife has had many miscarriages.

Case 8. Male, aged 60. **Part affected:** Tongue. **Duration:** $\frac{1}{12}$ year. **Physical condition:** Strong, heavily built man of definitely plethoric type. **Cardiovascular condition:** Artery wall markedly thickened and vessel somewhat tortuous. Arteries large and pulse tends to be collapsing. Heart seems healthy. Average systolic pressure 152 mm. Average diastolic pressure 106 mm. **Gout:** Well-marked and typical attacks of gout. I was able to observe two of these attacks, one of which occurred in hospital. The attacks began in big toe, which became red, tender, and inflamed, and thence spread to dorsum of the foot. He is largely disabled by the disease.

Case 9. Male, aged 54. **Part affected:** Tongue. **Duration:** $1\frac{6}{12}$ years. **Physical condition:** Small, thin, and much wasted when first seen. **Cardiovascular condition:** Artery at wrist somewhat thickened. P.M. The mitral valve showed numerous small, firmly adherent nodules, cultures from which proved sterile. The aorta showed little or no atheroma. Kidneys fairly healthy, with slight granular change. **Syphilis:** Probable six years ago.

Case 10. Male, aged 61. **Part affected:** Tongue. **Duration:** $\frac{1}{12}$ year. **Physical condition:** Wasted and cachectic when first seen. Has had good health. **Cardiovascular condition:** Arteries very slightly thickened. P.M. Old fibrous plaques on visceral pericardium. Slight atheroma of aorta. Kidneys show arterial thickening. **Syphilis:** Probable forty-two years ago. Wife had one child only, born dead.

Case 11. Male, aged 51. **Part affected:** Tongue. **Duration:** $\frac{3}{12}$ year. **Physical condition:** Well-nourished, very hearty looking man. **Cardiovascular condition:** Artery wall somewhat thickened. Heart appears to be sound. Average systolic pressure 141 mm. Average diastolic pressure 124 mm. **Gout:** Repeated attacks of pain in feet and legs sufficient to disable him for a day or two. In bad attacks pain and swelling spread to hands.

Case 12. Male, aged 58. **Part affected:** Tongue. **Duration:** $\frac{2}{12}$ year. **Physical condition:** Thin man, but strong and well nourished. Very good health. Has been in army and served in Egypt. **Cardiovascular condition:** Artery wall of radial vessel slightly thickened. Vessel large and big wave. Heart sound. Average systolic pressure 124 mm. Average diastolic pressure 95 mm. **Syphilis:** Had definite syphilis twenty-five years ago and took mercury for two months. Scar present on glans.

Case 13. Male, aged 51. **Part affected:** Tongue. **Physical condition:** Very well nourished sturdy man with congested venules on face and rather bibulous appearance. Obviously plethoric. Has been in the army and invalided with gout. Blood-count gave 4,750,000 reds. **Cardiovascular condition:** Radial artery somewhat thickened. Second aortic slightly accentuated and heart a little dilated. Average systolic pressure 150 mm. Average diastolic pressure 117 mm. **Gout:** Has been accustomed to have at least two or three

attacks of gout annually, and has been so for the last eighteen years. He has to keep off liquor as alcohol precipitates an attack. The attacks always begin in the big toe. There is marked fibrositis around the metatarso-phalangeal joints of the big toes and in certain finger-joints, and there are numerous tophi in the ears. I was able to observe an acute attack. The gout is hereditary. His father suffered from it in a severe form, and it caused his death.

Case 14. Male, aged 70. **Part affected**: Tongue. **Duration**: 3 years. **Physical condition**: Well-nourished stout man looking less than age. Plethoric. **Cardiovascular condition**: Artery walls are but slightly thickened. Heart a little dilated. Average systolic pressure 151 mm. **Syphilis** as a young man about forty-five years ago. Has had a sore tongue for the last sixteen years, and has often been troubled with ulcers on the tongue. Of his five children four have died very young, and his wife has had two miscarriages. **Gout**: Has had numerous typical attacks of gout commencing in big toe. Tophi in ears.

Case 15. Male, aged 75. **Part affected**: Tongue. **Duration**: 1 year. **Physical condition**: Very cachectic when first seen. Patient could hardly speak and history therefore difficult to obtain. **Cardiovascular condition**: All the arteries accessible to touch were found to be exceedingly thickened and tortuous. Heart dilated. P. M. Several fibrous plaques on visceral pericardium. Endocardium fairly healthy. Myocardium showed brown atrophy. The aorta was in an extreme condition of atheroma, its inner surface being absolutely covered with calcareous patches and ulcers. Kidneys showed well-marked interstitial fibrosis. **Remarks**: Aorta now in Museum of Cancer Hospital, New Series, No. 509.

Case 16. Male, aged 60. **Part affected**: Tongue. **Physical condition**: Very well-nourished stout man. High colour. Blood-count 4,563,000 reds. Occupied on heavy work in racing stables. **Cardiovascular condition**: Arteries slightly thickened. Large and rather sudden wave to pulse. Heart large, extending two fingers' breadths to left of the vertical nipple line. A soft systolic murmur at apex of heart conducted towards the left axilla. No murmur at aortic area. Average systolic pressure 174 mm. Average diastolic pressure 119 mm. **Syphilis** forty years ago; treated.

Case 17. Male, aged 69. **Part affected**: Tongue. **Duration**: $4\frac{6}{12}$ years. **Physical condition**: Wasted when first seen, but a tall well-built man, not however of a robust or plethoric type. Has had good health. **Cardiovascular condition**: Artery wall of radial vessel very much thickened, as is also brachial artery. Heart good. Vascular tension not raised. **Syphilis** thirty-six years ago. Scarring on body. **Remarks**: Growth clinically atypical, being of a papillomatous type and affecting tip. Microscopically there could be no doubt as to carcinomatous nature.

Case 18. Male, aged 54. **Part affected**: Tongue. **Physical condition**: Wasted and ill. Complexion muddy. Venules of face enlarged. **Cardiovascular condition**: Radial vessel thickened. Average systolic pressure 100 mm. Average diastolic pressure 80 mm. Severe haemorrhages the week before this observation was made. **Syphilis**: Had syphilis thirty years ago. Scarring now present on legs attributable to this. Wassermann negative. **Gout**: Has had very many attacks of gout, and always gets it in his big toe, chiefly of left foot. I was able to observe an attack which was quite typical. No tophi in ears.

Case 19. Male, aged 75. **Part affected**: Tongue. **Duration**: 1 year. **Physical condition**: Well-nourished old man of burly type, looking distinctly less than his age. Face congested. Appearance plethoric. Always had good health. **Cardiovascular condition**: Pulse full and strong, but radial vessel not markedly thickened for so old a subject. Some emphysema and general bronchitis. P. M. Fibrosis of mitral valves. Vessels remarkably good for so old a subject. Kidneys are moderately fibrotic. **Remarks**: Post-mortem appearances were by no means typical of epithelioma of the tongue. There was a widely spread glandular infection, and nodules of growths were extensively distributed in the submucous tissue throughout the lower pharynx. Microscopically there could be no doubt of carcinomatous nature of growth, which was very cellular and showed marked keratinization with little stroma.

Case 20. Male, aged 64. **Part affected**: Tongue. **Duration**: $\frac{5}{12}$ year. A wasted old man of great height. Anaemic and cachectic. **Cardiovascular condition**: Heart dilated to two fingers' breadths outside vertical nipple line. P. M. Mitral valves definitely thickened and showed some granulations. Aortic valves also had small old fibrous granulations. Aorta was only slightly atheromatous. Kidney — early interstitial nephritis — arteriosclerotic. **Syphilis**: Severe attack thirty years ago; treated.

Case 21.   Male, aged 50.   **Part affected**: Tongue.   **Duration**: $\frac{2}{12}$ year.   **Physical condition**: Powerfully-built man. High florid colour. 'Never been laid up, and never had a day's illness in his life.' Has been a policeman, and since leaving force has been doing painter's work.   **Cardiovascular condition**: Walls of peripheral vessels definitely thickened and tortuous. Systolic pressure 126 mm. Diastolic pressure 102 mm.

Case 22.   Male, aged 66.   **Part affected**: Tongue.   **Physical condition**: Thin old man, not wasted or cachectic. Post office for thirty-three years.   **Cardiovascular condition**: Radial vessel degenerate, hard and tortuous. The vessels in the upper arm and at the elbow exhibit even more marked degeneration. The deep cardiac dullness is much enlarged downwards and to the left, but not much outwards. There is a soft systolic murmur at the apex which is traceable towards the axilla.   **Syphilis**: Had syphilis thirty years ago since birth of his only child. Wife has had no pregnancies since. Wassermann negative.   **Gout**: Had an attack eight years ago in the feet and was laid up for ten weeks. Some time after he was again laid up and several attacks since. Condition of metatarso-phalangeal joints suggests old gouty changes.

Case 23.   Male, aged 67.   **Part affected**: Tongue.   **Physical condition**: Big, heavily built, powerful man who has been in army and served in India. Never laid up until a year before admission (see Remarks).   **Cardiovascular condition**: Radial and brachial vessels markedly thickened and tortuous. Well-marked emphysema. A ring of enlarged vessels at line of attachment of diaphragm.   **Syphilis** about fifty years ago and was treated for it.   **Remarks**: A medical practitioner writes to me that a year before I saw this patient he treated him for 'ascites due to cirrhosis of the liver'. He had also albumiuuria. He has been a heavy drinker.

Case 24.   Male, aged 65.   **Part affected**: Tongue.   **Physical condition**: Well nourished. Looks his age. Suffers a great deal with eczema and accompanying conjunctivitis. Well-marked arthritic condition, probably osteoarthritis.   **Cardiovascular condition**: Artery walls not thickened. Heart sound.   **Remarks**: Hands show well-marked arthritic changes. There are 'Heberden's nodes' towards the last joint, best marked on forefinger but also present on others. In several of the joints there are little herniae of synovial membrane which can be reduced on pressure. No tophi. Has suffered repeatedly with generalized eczema.

Case 25.   Female, aged 52.   **Part affected**: Tongue.   **Duration**: 4 years ?   **Physical condition**: Well-nourished stout woman. Face puffy. Never been laid up except in confinement. Change of life age, 49. Excellent health.   **Cardiovascular condition**: Radial artery large and pulse full, but tension not markedly raised, nor is the wall thickened or tortuous.   **Syphilis**: Patient has had five miscarriages, but no other history of syphilis can be obtained.

Case 26.   Male, aged 50.   **Part affected**: Tongue.   **Duration**: $1\frac{3}{12}$ years.   **Physical condition**: Has evidently been a powerful man, though now wasted and cachectic. Has been a heavy drinker. Occupation, brewer's labourer.   **Cardiovascular condition**: Arteries extremely degenerate, hard and tortuous. Tension not obviously raised, but difficult to measure, owing to extreme arteriosclerosis. Heart sounds very faint.   **Syphilis**: No history of syphilis, but has had gonorrhoea several times and history difficult to elicit. All his three children died in the first few days of life.

Case 27.   Male, aged 49.   **Part affected**: Tongue.   **Duration**: $\frac{3}{12}$ year.   **Physical condition**: Well nourished, of plethoric type, with injected venules on face. Occupation, lighterman and bargee. Heavy drinker, never laid up.   **Cardiovascular condition**: Arteries at wrist distinctly thickened and tortuous and tension raised. Heart is healthy.   **Syphilis**: Denies syphilis. Gonorrhoea thirty years ago. Pupils unequal and small, but react to light. Knee-jerks present and brisk.

Case 28.   Male, aged 49.   **Part affected**: Tongue.   **Duration**: $\frac{2}{12}$ year.   **Physical condition**: Has evidently been a powerful man, though wasted when first seen. He says 'I have never known my own strength', and has had exuberant health. Has been a stevedore.   **Cardiovascular condition**: Walls of arteries in arm are greatly thickened. P. M. Numerous fibrous plaques on visceral pericardium. Ascending aorta dilated, and aorta showed advanced atheroma. Lungs emphysematous. Kidneys: Cortex diminished, capsule adherent, microscopically some patchy fibrosis.   **Syphilis** thirty years ago, which was not properly treated. Though married he has had no children. No history of miscarriages.   **Gout**: Suffered a good deal with gout, diagnosed at hospital where he attended for some time for treatment. The attacks begin in the big toe, which he described as swelling and becoming shiny. The swelling gradually spreads to the foot. Numerous attacks.

Case 29. Male, aged 56. **Part affected**: Tongue. **Duration**: $\frac{6}{12}$ year. **Physical condition**: A very large stout man, immensely muscular and of a typically apoplectic appearance. He is a sailor. **Cardiovascular condition**: The accessible arteries not markedly thickened. The second aortic sound definitely accentuated. **Syphilis** thirty-two years ago. There is now a scaly and pigmented generalized rash. Wassermann negative. **Remarks**: Tongue in Museum of Cancer Hospital, New Series, No. 554.

Case 30. Male, aged 66. **Part affected**: Tongue. **Duration**: $\frac{4}{12}$ year. **Physical condition**: Well-nourished and muscular old man. Labourer. Never been laid up in his life except with gout. **Cardiovascular condition**: Arteries in arms are large, thick, and tortuous. Heart sounds very faint. **Gout**: Has had repeated attacks of gout, nine or ten of them severe. ' Sometimes my big toe swells so that I can't get my boot on.' He has tophi in the ears, and there is a well-marked tophaceous deposit in right forefinger. The gout commenced about fourteen years ago. Both big toes have at times been involved, and in the bad attacks the pain and swelling spreads to hands.

Case 31. Male, aged 62. **Part affected**: Tongue. **Physical condition**: Very healthy man. ' I don't know what it is to have a day's illness.' Is a plumber, but no history of lead poisoning. **Cardiovascular condition**: Artery wall at wrist distinctly tortuous and thickened. Relative cardiac dullness extends to or beyond nipple. Cardiac sounds faint. Soft systolic murmur at base. **Syphilis**: Venereal disease thirty years ago and ' reminders ' ever since. Suffered a great deal with sore throats. Scar present on penis. His wife has borne five still-born children and had several miscarriages.

Case 32. Male, aged 52. **Part affected**: Tongue. **Duration**: $\frac{3}{12}$ (?) year. **Physical condition**: Very strong muscular subject—looks more than his years. Well-marked arcus senilis. Has had extremely good health except for gout. **Cardiovascular condition**: Radial vessel large and its wall markedly thickened. Tension raised. Second sound a little accentuated at base. **Gout**: Has had a number of attacks of gout affecting his toe and ankle. Had a subacute attack in hospital which I was able to observe. No tophi in ears.

Case 33. Male, aged 52. **Part affected**: Tongue. **Duration**: 2 years. **Physical condition**: Well-nourished, powerful, full-blooded man. Has never had a day in bed since youth. Works a good deal as barman and as a dock labourer. **Cardiovascular condition**: The pulse is markedly irregular in both force and frequency, averaging about 90 beats per minute. The radial vessel is very thickened and tortuous. Chest definitely emphysematous and barrel-shaped. **Syphilis**: Wife has had two miscarriages, followed by two healthy children.

Case 34. Male, aged 61. **Part affected**: Tongue. **Duration**: 3 years. **Physical condition**: Markedly wasted when first seen, but has evidently been a powerful man and says he has never had an illness sufficient to lay him up. **Cardiovascular condition**: The radial artery extremely thickened and tortuous. Some emphysema and bronchitis. P. M. Some cardiac hypertrophy. Early atheroma of aorta. Kidneys small and arteriosclerotic. **Syphilis**: Probably none. Wife has had three living and healthy children and no miscarriages.

Case 35. Male, aged 53. **Part affected**: Tongue. **Duration**: $\frac{1}{12}$ year. **Physical condition**: Well nourished, but looks rather more than age. **Cardiovascular condition**: Radial and other vessels are very thickened and tortuous. Heart dullness percussed an inch or more external to the left nipple. Sounds faint. There is a soft systolic murmur over the praecordium not distinctly conducted to axilla.

Case 36. Male, aged 50. **Part affected**: Tongue. **Duration**: $1\frac{6}{12}$ years. **Physical condition**: Very cachectic when first seen. Has had good health except for gout. His occupation has been that of a cellarman. **Cardiovascular condition**: The arteries of the limbs are very tortuous, hard, and thickened. The deep cardiac dullness extends an inch to the left of the nipple. The heart-beat is distinctly irregular. Fairly marked emphysema. Chest of rickety type. P. M. Extensive old pericardial adhesions and visceral pericardial plaques. Cardiac hypertrophy. Patchy myocardial fibrosis. Kidney: Irregular cortical areas of fibrosis. **Gout**: Has had a number of attacks of gout, during which ' his hands and feet have swelled and lumps have come up on his knuckles '. No tophi in ears, but gouty changes well marked in hands. A medical man who knows him well writes to me that he has ' attended him several times during the last ten years suffering from acute attacks of gout, attributed chiefly to his employment as cellarman '.

Case 37. Male, aged 72. **Part affected:** Tongue. **Duration:** 6 years. **Physical condition:** Wiry, slightly-built man, with very high colour and weathered appearance. Thirty years ago a doctor said he had consumption, but he got better and otherwise has had good health. **Cardiovascular condition:** Radial vessel degenerate, tortuous, and thickened. Pulse 80, slightly irregular. A faint systolic murmur at the aortic area. P. M. Cardiac hypertrophy. Atheroma of aorta, increasing in abdominal aorta and well marked at bifurcation. Kidney showed microscopically some interstitial fibrosis. **Rheumatism:** Rheumatoid disease in right elbow and shoulder of old standing.

Case 38. Male, aged 47. **Part affected:** Tongue. **Duration:** $\frac{8}{12}$ year. Well nourished and still powerful, though he says he has lost flesh a good deal. 'I have had wonderfully good health and never had a day in bed.' **Cardiovascular condition:** The radial vessel is somewhat thickened and tortuous. Heart quite sound. **Gout:** Attacks of gout of late years with pain in big toe from time to time. Well-marked tophi in ears.

Case 39. Male, aged 69. **Part affected:** Tongue. **Duration:** 3 years. **Physical condition:** Shows signs of having been a powerful man, though now much wasted. He is well built and muscular, but muscles hang loosely on limbs. He used to weigh 14 stone when a younger man. Heavy beer-drinker. Has suffered a good deal with bronchitis. **Cardiovascular condition:** The blood-vessels at the wrist greatly thickened and tortuous. Heart sounds very faint. **Syphilis (?):** His two children died as infants. Wife had no miscarriages (?).

Case 40. Male, aged 63. **Part affected:** Tongue. **Duration:** $\frac{3}{12}$ year. **Physical condition:** Small, thin, little man of poor physique, but in spite of this has 'never been laid up'. **Cardiovascular condition:** Heart small, healthy. Vessels of arm are extremely thickened and tortuous. Bronchitis and emphysema. P. M. Heart small; healthy kidneys, present well-marked patchy interstitial fibrosis. These organs were small and granular.

Case 41. Male, aged 68. **Part affected:** Tongue. **Duration:** $\frac{8}{12}$ year. **Physical condition:** Wasted when first seen. Never ill except with gout. Puffy appearance suggesting Bright's disease. **Cardiovascular condition:** Radial vessel not markedly degenerate, but the brachial vessel presents well-marked changes, and is hard and tortuous. Tension raised. The heart is distinctly enlarged, and its deep dullness is well outside the left nipple. There is a soft systolic murmur over the praecordium traceable into the neck. There are very well-marked emphysematous changes in the chest and the air entry is very poor. P. M. Heart hypertrophied and weighed 18 ounces. Mitral valves a good deal thickened and calcified. Advanced atheroma of thoracic aorta with calcareous plaques. Arteries of second degree showed only patchy intimal changes. Lungs very emphysematous. Kidneys small (4 and $4\frac{1}{2}$ oz.), congested, increase in pelvic fat, granular and many small cysts. Microscopically the kidneys showed areas of fibrosis, especially round the glomeruli, some of which were completely sclerosed. In radial artery nodular intimal hypertrophy was demonstrated. **Gout:** Has had many attacks of gout of a mild form. Tophi in ears. Arthritic changes in hands. Entropion.

Case 42. Male, aged 43. **Part affected:** Tongue. **Duration:** $\frac{5}{12}$ year. **Physical condition:** Very cachectic when first seen. **Cardiovascular condition:** Radial and brachial artery wall very thickened and tortuous. Heart good. P. M. Numerous metastases in heart wall. Vegetation on mitral valve. Aorta showed slight atheroma. Coronaries considerably diseased. Kidneys healthy. **Syphilis:** Definite history of syphilis. Treated for fifteen months.

Case 43. Male, aged 52. **Part affected:** Tongue. **Duration:** $1\frac{6}{12}$ years. **Physical condition:** Very cachectic. **Cardiovascular condition:** Radial and brachial vessels very thickened and tortuous. Deep cardiac dullness extended $\frac{1}{2}$-1 in. outside nipple line. Soft systolic murmur at apex not conducted towards axilla. P. M. Cardiac dilatation and hypertrophy. Valves healthy. Aorta extensively atheromatous. Coronaries good. Kidneys small with capsule adherent in parts, cortex thinned and pelvic fat increased. Microscopically some patchy fibrosis. **Syphilis (?):** Twenty-five years ago.

Case 44. Male, aged 66. **Part affected:** Tongue. **Duration:** 1 year. **Physical condition:** A very muscular, sturdy, full-blooded man. Though very short he weighs 10 st. 11 lb. He is manifestly very robust, and says, 'Except for the gout I have never been laid up at all.' Is a cooper. **Cardiovascular condition:** The radial vessel is distinctly thickened and tortuous. In spite of the great muscular development and good supply of subcutaneous tissue the brachial

vessel can be both seen and felt to be tortuous all the way up the upper arm. Heart sounds faint and slightly irregular. **Gout**: Has had five bad attacks of gout, besides many minor ones. No tophi in ears, but gouty changes in hands. His doctor writes to me thus: 'For the last eight years he has been subject to attacks of gout two or three times a year in the feet and knees. The attacks have been acute, but did not last long, and he was generally able to resume his work in a week. The last attack continued for three weeks and did not quite leave him till he had a change of air. His brother was a martyr to gout and died from its effects. Another brother . . . had gout as a young man, but it left him in later life.'

Case 45. Male, aged 46. **Part affected**: Tongue. **Duration**: $1\frac{6}{12}$ years. **Physical condition**: Fairly well nourished when first seen, though he assured me he had lost three stone. He must have been a very big heavy man. Very good health. He has been in the army and has seen much foreign service. Has never been laid up. **Cardiovascular condition**: Radial vessel large and somewhat tortuous. Heart good. P. M. Slight mitral sclerosis. Myocardium streaky. Aorta and arteries good. **Syphilis**: Probable. He has what appears to be a tertiary syphilide, and though he denies syphilis his army history makes it probable. Wife had no children or miscarriages.

Case 46. Male, aged 63. **Part affected**: Tongue. **Duration**: $\frac{10}{12}$ year. **Physical condition**: Well nourished and sturdy, though of short stature. Has had good health. **Cardiovascular condition**: Artery wall at wrist and in arm distinctly thickened and tortuous. Pulse tension slightly raised. There is a short systolic murmur at aortic area. P. M. Cardiac hypertrophy. Atheroma of aortic valves with patches of calcareous degeneration. Larger vessels healthy. Emphysema. Kidneys had a granular surface and showed microscopically considerable chronic diffuse nephritis. **Syphilis**: Probable. Wife has had several miscarriages. **Gout**: There are definite tophi in ears. He has had a number of attacks of gout which usually lay him up for about a week. The attacks of gout usually commence in the great toe.

Case 47. Male, aged 41. **Part affected**: Tongue. **Duration**: $\frac{5}{12}$ year. **Physical condition**: Has been a very powerful man, has always had good health, and has never been laid up. Blacksmith. **Cardiovascular condition**: Artery at wrist markedly tortuous and thickened, as is also the vessel at the bend of the elbow and in the upper arm. Heart sound. P. M. A little cardiac hypertrophy. Aorta healthy. Chronic diffuse nephritis. Lungs present a state of chronic pneumonia. **Remarks**: Definite history of jagged tooth causing irritation.

Case 48. Male, aged 54. **Part affected**: Tongue. **Duration**: $\frac{9}{12}$ year. **Physical condition**: A largely-built, heavy man. Very high colour and plethoric appearance. Has had very good health. Publican and hard drinker, but has been forced to be temperate of late years on account of attacks of gout. **Cardiovascular condition**: Vessels of arm thickened and slightly tortuous. Heart apparently healthy. **Syphilis** twenty-seven years ago, and was treated for three years at the Lock Hospital and elsewhere. Had much mercury, but was never salivated. Attack was a severe one, but he has had no 'reminders'. **Gout**: Has had a typical attack of gout one year ago, commencing in big toe and lasting, or rather hanging about, for a month. A medical man who treated him at the time writes to say that he diagnosed gout. The patient has also had some minor attacks.

Case 49. Male, aged 66. **Part affected**: Tongue. **Duration**: 25 years? **Physical condition**: Fine, muscular, well-developed man. Has been in army in India and elsewhere. **Cardiovascular condition**: Arteries fairly good. Only first cardiac sound can be heard. P. M. Sclerosis of mitral valve. Advanced aortic atheroma, most marked at arch. Numerous small ulcers and calcareous plaques, some of the larger ulcers showing puckered edges. A good deal of disease in coronary arteries and carotids. Lungs showed advanced emphysema. **Syphilis** denied. Married twice and no miscarriages by either wife.

Case 50. Male, aged 41. **Part affected**: Tongue. **Physical condition**: Emaciated and cachectic when first seen. Has been a very hard drinker. **Cardiovascular condition**: Radial and brachial vessels very thickened and tortuous. Cardiac sounds faint. P. M. Numerous old fibrous plaques on pericardium. Heart hypertrophied. Aorta moderately atheromatous. Multilobular cirrhosis of liver. **Gout**: Indefinite symptoms. Many nodules along margin of helix. **Remarks**: A medical practitioner writes that he has known him for some years as an alcoholic.

Case 51. Male, aged 68. **Part affected**: Tongue. **Duration**: $\frac{4}{12}$ year. **Physical condition**: Big, strong man. Has been in army. Very good health. **Cardiovascular con-**

dition : Peripheral vessels not thickened or tortuous and tension not raised.   Heart somewhat enlarged.   Heart sounds faint.   Second aortic sound accentuated at base.   P. M. The most extreme degree of atheroma of aorta.   Well-marked chronic changes in lungs, with fibrosis, emphysema, and pigmentation.   Early chronic nephritis.   Heart healthy.   **Syphilis** forty-six years ago.   **Remarks :** Hemiplegic attack five years ago.   One child, 17 years old, healthy.   Wife has had no miscarriages.

Case 52.   Male, aged 62.   **Part affected :** Tongue.   **Duration :** 3 years.   **Physical condition :** Very strong, heavily-built man, well nourished and muscular.   **Cardiovascular condition :** Pulse 70, markedly irregular in force and frequency, with frequent interpolated beats.   Peripheral vessels large, nodular, thickened and tortuous.   Marked accentuation of aortic second sound.   **Rheumatism :** Rheumatic fever as a young man.   **Remarks :** Wife died of cancer of the uterus.

Case 53.   Male, aged 49.   **Part affected :** Tongue.   **Duration :** 3 years.   **Physical condition :** Wasted and cachectic, but has evidently been a big, strong man.   Has been in army and has had extremely good health.   **Cardiovascular condition :** Radial vessel soft and not thickened.   The brachial artery shows slight signs of arteriosclerotic change.   P. M. Cardiac hypertrophy.   Aorta fairly healthy.   Kidneys present thickening of capsule and patchy fibrosis.   Coarse fibrosis of liver.   Pulmonary emphysema, pigmentation, and fibrosis.   **Syphilis** thirty-three years ago when 16 years old.   The attack was a very severe one, and has left numerous scars all over body.   He was treated for one year.   Wife pregnant once only, resulting in a miscarriage.   A scar present on glans.   **Remarks :** Wife died nine years ago of cancer of the stomach (microscopic evidence).

Case 54.   Male, aged 47.   **Part affected :** Tongue.   **Duration :** $\frac{2}{12}$ year.   **Physical condition :** Burly, full-blooded, red-faced man.   **Cardiovascular condition :** Vessels in upper arm and in temporal region sclerotic.   A loud aortic systolic murmur and accentuated aortic second sound.   Chest barrel-shaped.   Well-marked emphysematous changes.   **Remarks :** An illness with well-marked rash, which lasted for some time, twenty-five years ago.   Wife had one miscarriage.   No definite evidence of syphilis.

Case 55.   Male, aged 51.   **Part affected :** Tongue.   **Duration :** $1\frac{6}{12}$ years.   **Physical condition :** Short, stout, heavily-built man, of high colour and sturdy frame.   Painter and gas-fitter.   **Cardiovascular condition :** Heart and vessels appear healthy.   Chest of emphysematous form.   **Syphilis :** Definite syphilis twenty-nine years ago, with rash, scar, and sore throat.   Treated for eight months.   Wife has had one still-born child, one miscarriage, and one healthy child.   **Remarks :** Has had a 'sore tongue' on and off for the last twenty-one years.

Case 56.   Male, aged 69.   **Part affected :** Tongue.   **Duration :** $\frac{2}{12}$ year.   **Physical condition :** Big, heavily-built man, weighing 13 stone.   **Cardiovascular condition :** All arteries accessible to touch seem markedly sclerotic.   Cardiac sounds very faint.   Pulse 84.   The chest wall is very rigid and typically emphysematous.   **Gout :** Has had a number of attacks of gout affecting both hands and feet.   I observed a well-marked acute attack affecting the metacarpophalangeal joint of the forefinger of the left hand.   No tophi.   Dupuytren's contracture.

Case 57.   Male, aged 58.   **Part affected :** Tongue.   **Duration :** $\frac{5}{12}$ year.   **Physical condition :** Spare man, but muscular and of weathered appearance.   Postman.   Has had very good health.   **Cardiovascular condition :** Artery walls at wrist and in upper arms tortuous and thickened.   Cardiac sounds faint.   Chest emphysematous, with ring of enlarged blood-vessels along line of attachment of diaphragm.   **Gout :** Had a typical attack of gout three years ago, diagnosed by a medical man.   The attack was localized in big toe and prevented him going his rounds for some weeks.

Case 58.   Male, aged 53.   **Part affected :** Tongue.   **Duration :** $\frac{3}{12}$ year.   **Physical condition :** Well-built, sturdy, thick-set man.   **Cardiovascular condition :** Heart and vessels appear healthy.   Chest somewhat barrel-shaped.   **Syphilis** twenty-four years ago.   Wassermann positive.

Case 59.   Male, aged 62.   **Part affected :** Tongue.   **Duration :** $\frac{3}{12}$ year.   **Physical condition :** Feebly developed.   **Cardiovascular condition :** Heart and arteries appear to be healthy.   **Syphilis** forty years ago.   **Remarks :** Has had attacks of 'smoker's tongue' for the last twenty years, although he is not a very heavy smoker.   His wife died of cancer of the uterus (verified from records) preceded by miscarriage.

Case 60. Male, aged 58. **Part affected:** Tongue. **Physical condition:** Big man with weathered appearance. Suffers from acne rosacea. **Cardiovascular condition:** The peripheral arteries are very sclerosed and tortuous, and there is also well-marked sclerosis of the veins. The second sound can only be heard at the apex. Back bowed and chest wall has very limited movement.

Case 61. Male, aged 48. **Part affected:** Tongue. **Duration:** $\frac{3}{12}$ year. **Physical condition:** Rather poorly developed. Has been in army. **Cardiovascular condition:** Heart and arteries appear to be healthy. **Syphilis** in Straits Settlements twenty-five years ago.

Case 62. Male, aged 53. **Part affected:** Floor of mouth. **Duration:** $1\frac{5}{12}$ years. **Physical condition:** Pale, unhealthy-looking man. Well nourished. **Cardiovascular condition:** Arteries very good. No obvious thickening and tension not raised. **Syphilis** nineteen years ago. Treated for nine months.

Case 63. Male, aged 56. **Part affected:** Floor of mouth. **Duration:** 2–4 years. **Physical condition:** Unhealthy-looking man. Acne and angiomata on nose give a bibulous appearance. Well nourished. **Cardiovascular condition:** Radial artery somewhat thickened.

Case 64. Male, aged 41. **Part affected:** Floor of mouth. **Duration:** 1 year. **Physical condition:** Very well nourished man. Stands 6 ft. high and is stout, strong, and muscular. **Cardiovascular condition:** Artery wall at wrist definitely thickened. Heart sound. **Rheumatism:** Rheumatic fever twice.

Case 65. Male, aged 56. **Part affected:** Floor of mouth. **Duration:** $\frac{9}{12}$ year. **Physical condition:** Well developed, but has lost much flesh. Looks more than his age. His hair is quite white and there is a very marked arcus senilis. Very good health and has been in army. Blacksmith. **Cardiovascular condition:** Artery walls where accessible to touch are very much thickened and tortuous. The peripheral vessels are large and can be seen writhing in the upper arms synchronously with heart-beat. Tachycardia. No shortness of breath and no cardiac lesion. Pulse 116. **Syphilis** twenty-nine years ago in Cyprus.

Case 66. Male, aged 49. **Part affected:** Floor of mouth. **Duration:** $\frac{11}{12}$ year. **Physical condition:** Wasted and cachectic, but says, 'I have never been ill in my life and have always been a strong man.' **Cardiovascular condition:** The artery walls of the upper limbs are tortuous and very markedly thickened. Heart sound. P.M. Heart muscle, cardiac valves, aorta, and kidneys healthy.

Case 67. Male, aged 61. **Part affected:** Floor of mouth. **Duration:** $\frac{1}{12}$ year. **Physical condition:** Fair development. **Cardiovascular condition:** Peripheral arteries much thickened. **Remarks:** History of rheumatoid disease. Well-marked chronic articular changes.

Case 68. Male, aged 49. **Part affected:** Inner side of cheek. **Physical condition:** Stout, heavily built man. Has been a painter, and though no history of lead poisoning can be obtained, he has every evidence of arterial degeneration. Has been a very heavy drinker. Plethoric appearance. **Cardiovascular condition:** Patient is hemiplegic, the right arm and leg being affected. The hemiplegic attack came on quite suddenly when patient was in good health, and before the appearance of the epithelioma of the cheek. Vessel wall at wrist only slightly thickened, but of obviously high tension to the examining finger. Systolic pressure 162 mm. Diastolic pressure 107 mm. Heart somewhat dilated and accent on second sound at the aortic and pulmonary areas. Patient is markedly emphysematous. **Syphilis:** Well-marked attack of syphilis thirty-one years ago and was treated for only two months. **Gout:** Had repeated attacks of gout for many years and of the severest type. The attacks commenced first in the big toe, but gradually spread to other parts, hands, elbows, knees. Well-marked tophi in ears and gouty changes in joints of hand. I have observed three attacks of gout in this patient. Father was for years disabled by gout and died of it, aged 42. **Remarks:** Specimen in Museum of Cancer Hospital, New Series, No. 498.

Case 69. Male, aged 48. **Part affected:** Inner side of cheek. **Physical condition:** Well nourished, but lost flesh before admission. **Cardiovascular condition:** Slight enlargement of heart to the left. Pulse not high tension. **Syphilis:** Well-marked attack of syphilis twenty-nine years ago. Treated for one year.

Case 70. Female, aged 49. **Part affected:** Tonsil. **Duration:** $1\frac{3}{12}$ year. **Physical condition:** Thin brunette. Has always been slight, always very good health, and says she has never consulted a doctor in her life, except for childbed. Change of life age, 48. **Cardio-**

vascular condition : Radial and brachial vessels very distinctly thickened and tortuous, second sound distinctly accentuated at aortic area, and first sound at apex blurred. **Syphilis** : Has had four pregnancies. Of these one was a miscarriage, one was a seven months' child which died at birth, one died aged 7 of 'croup', and the other is living. No history of syphilis.

Case 71. Male, aged 51. **Part affected** : Tonsil. **Duration** : 2 years. **Physical condition** : Largely built, heavy, muscular man. **Cardiovascular condition** : Peripheral vessels thickened but not tortuous. Heart a little enlarged. A soft systolic murmur best heard at apex.

Case 72. Male, aged 67. **Part affected** : Tonsil. **Duration** : $\frac{6}{12}$ year. **Physical condition** : Well-built, muscular man. Has been in army. **Cardiovascular condition** : Slightly irregular pulse. Slight tortuosity and thickening of vessels. Heart sounds very faint. **Syphilis** in India forty-seven years ago. Wife has had two miscarriages.

Case 73. Male, aged 47. **Part affected** : Lower jaw. **Duration** : $\frac{6}{12}$ year. Big, heavy, muscular subject, of plethoric type. Bus-driver. Has had very good health, and has not been away from work for twenty-seven years. **Cardiovascular condition** : Artery walls not thickened. Cardiac sounds good. Nil adventitious. P. M. Heart fairly good. Aorta presents fairly marked atheroma. Definite chronic interstitial nephritis. Emphysema. Early portal cirrhosis.

Case 74. Male, aged 69. **Part affected** : Palate. **Physical condition** : General nutrition excellent. **Cardiovascular condition** : Radial vessel distinctly thickened and tension raised. P. M. Slight thickening of mitral valves. At arch of the aorta were several calcareous plates. These increase as one descends downwards, so that the whole of the abdominal aorta is calcareous. Kidneys healthy.

Case 75. Male, aged 50. **Part affected** : Palate. **Duration** : $\frac{11}{12}$ year. **Physical condition** : Powerful, well-nourished man still, though he says he has lost much flesh. Porter. **Cardiovascular condition** : Vessels throughout arm and forearm very distinctly thickened and tortuous. At wrist the vessel is almost stony-hard. An occasional missed beat, second sound accentuated at base of heart. P. M. Old fibrous plaques on pericardium. Some mitral sclerosis. Moderate aortic atheroma extending into carotids. Kidneys small, $4\frac{1}{4}$ oz. and $3\frac{1}{2}$ oz., with a moderate amount of interstitial fibrosis. **Rheumatism** as a child. **Remarks** : History of dropsy of renal origin.

Case 76. Male, aged 39. **Part affected** : Upper jaw. **Physical condition** : Fairly well nourished and developed. 'Never lost a day's work.' **Cardiovascular condition** : Arteries slightly thickened. Soft systolic murmur at apex (? haemic).

Case 77. Female, aged 50. **Part affected** : Upper jaw. **Duration** : 2 years. **Physical condition** : Very robust and well nourished. Has had very good health. **Cardiovascular condition** : Radial vessel not markedly thickened. Average systolic pressure 120 mm. Average diastolic pressure 92 mm. **Remarks** : Dates onset from menopause.

Case 78. Female, aged 64. **Part affected** : Upper jaw. **Duration** : $\frac{6}{12}$ year. **Cardiovascular condition** : Fairly advanced general thickening of peripheral arteries. First sound a little blurred at apex and second sound slight, accentuated at aortic area.

Case 79. Male, aged 61. **Part affected** : Carcinoma of lip. **Physical condition** : Large, heavy, well-built man, well nourished. **Cardiovascular condition** : Radial and brachial arteries distinctly hard and thickened, but not tortuous. **Syphilis** forty-two years ago. Treated. Many scars remain on body.

Case 80. Male, aged 70. **Part affected** : Lip. **Duration** : $1\frac{6}{12}$ years. **Physical condition** : Well preserved, looks less than his age. No arcus senilis. Has been a very strong man, and employed for twenty-three years as a warder at a convict prison. Good health. **Cardiovascular condition** : Radial and brachial vessels greatly thickened and tortuous.

Case 81. Male, aged 59. **Part affected** : Lip. **Duration** : 5 years or more. **Physical condition** : Very muscular and powerful man and of fine physique. **Cardiovascular condition** : Wall of radial and brachial vessels not obviously thickened. Some emphysema. **Syphilis** : Probable. He denies syphilis, but he is an unmarried man and admits gonorrhoea with a rash for about a fortnight thirty years ago. He has now a number of unaccountable scars on his body. Has suffered a good deal with a scaly condition of the scalp, remains of which can still be seen in the corona veneris area. He has a widely-spread psoriasis-like rash.

E 2

Case 82. Male, aged 74. **Part affected:** Carcinoma originating on inner side of lower lip. **Duration:** 2 years. **Physical condition:** Very well nourished and looking less than his age. Says he has never taken a day off work since 8 years of age, and has always had heavy work on a farm. **Cardiovascular condition:** Radial and brachial arteries markedly degenerate. Heart definitely dilated. Accentuated aortic second sound which has an echoing quality. Average systolic pressure, 162 mm.

Case 83. Male, aged 71. **Part affected:** Lip. **Duration:** 9 years. **Physical condition:** Alert, upright, and well nourished, in spite of age. In addition to growth on lip there is an extensive leukoplakia of cheeks and tongue. 'Never been ill in his life' sufficient to keep him his bed. **Cardiovascular condition:** Artery wall good and not more thickened than might be expected in a man of 71 years. Heart good. Poor air entry into chest and some general bronchitis. **Syphilis** forty years ago. Has had children both before and since the attack, but wife had no miscarriages. **Remarks:** Rheumatoid changes in hands and feet.

Case 84. Male, aged 61. **Part affected:** Lip. **Duration:** $1\frac{6}{12}$ years. **Physical condition:** Well nourished, heavy man, of the brewer's drayman type. 'Never had anything worse than the toothache in his life.' **Cardiovascular condition:** Radial vessel considerably thickened and tortuous. Emphysematous chest. P. M. Cardiac hypertrophy. Myocardium and valves healthy. Patchy atheroma of thoracic aorta. This condition was more marked in abdominal aorta and extreme at bifurcation. Kidneys showed microscopically slight interstitial nephritis. **Syphilis:** No history. Wassermann negative. **Remarks:** Pipe smoker. History of habit of rubbing lip against pipe stem in region of onset of growth very definite.

Case 85. Male, aged 51. **Part affected:** Lip. **Duration:** 1 year. **Physical condition:** Small, frail man, not wasted. **Cardiovascular condition:** Arteries and heart good.

Case 86. Male, aged 68. **Part affected:** Lip. **Duration:** 3 years. **Physical condition:** Well-nourished, powerful, and muscular man. Stout. Looks less than age. Gardener. Good health. Very rarely laid up, except with gout. **Cardiovascular condition:** Arteries and heart good. Radial vessel large but hardly thickened. Heart sounds faint. **Gout:** Has had a typical attack of gout, commencing in big toe, some years ago. He was laid up with it for a couple of weeks. Has also had minor attacks. **Remarks:** Definite history of irritation by use of bluestone on a cracked lip for years.

Case 87. Male, aged 58. **Part affected:** Lip. **Duration:** $\frac{4}{12}$ year. **Physical condition:** Well-nourished plethoric type. **Cardiovascular condition:** Artery walls at wrist seem somewhat thickened, but not those in upper arm. There is a double murmur of aortic origin at the base of the heart. **Syphilis** thirty years ago. Tertiary symptoms in larynx.

Case 88. Male, aged 54. **Part affected:** Lip. **Duration:** $2\frac{3}{4}$ years. **Physical condition:** A well-nourished, powerful, muscular man. Has had very good health. Never laid up. Farm labourer. **Cardiovascular condition:** Radial vessel large and distinctly thickened and somewhat tortuous. The vessel in the upper arm is more markedly degenerated. Heart good. **Syphilis** thirty-eight years ago when only 16. Not treated. Wife had numerous miscarriages and died 'in a fit'. **Remarks:** A benign papilloma was present on the tongue.

Case 89. Female, aged 58. **Part affected:** Lip. **Duration:** $\frac{4}{12}$ year. **Physical condition:** Cachectic when first seen. **Cardiovascular condition:** Radial vessel thickened and tortuous, but the degenerative change is much more marked in the upper arm. P.M. Heart and endocardium healthy. Vessels, as far as they were examined, good. Kidneys typically arteriosclerotic and microscopically much fibrosis around vessels. **Syphilis:** Two miscarriages. No children. Husband in army. No other evidence. **Remarks:** A sister now in hospital with cancer of the breast.

Case 90. Male, aged 43. **Part affected:** Lip. **Duration:** 2 years. **Physical condition:** Slightly-built man. Very good health and has only been away from work for three weeks in thirty years. **Cardiovascular condition:** Pulse irregular. Considerable thickening of peripheral vessels.

Case 91. Male, aged 68. **Part affected:** Lip. **Duration:** $2\frac{1}{2}$ years. **Physical condition:** Feeble physique, but has had very good health. **Cardiovascular condition:** Vessels not thickened. Cardiac sounds faint. **Remarks:** Very moderate smoker and uses only wooden pipes.

Case 92. Male, aged 61. **Part affected:** Lip. **Duration:** $\frac{3}{12}$ year. **Cardiovascular**

condition : Heart and arteries appear to be healthy. **Syphilis** thirty-four years ago. **Gout** : Has had four attacks of gout which have always started in big toe and have lasted about a week. **Remarks** : Heavy pipe smoker.

Case 93. Male, aged 37. **Part affected** : Lip. **Duration** : $\frac{3}{12}$ year. **Physical condition** : Well-nourished, powerful man, high colour and sturdy build. Agricultural labourer. **Cardiovascular condition** : Arteries are distinctly thickened and tortuous, the changes being better marked in the upper arm than in the forearm. Chest of emphysematous type.

APPENDIX B.

Non-oral Cases with Syphilitic History or Signs.

Case 1. Male, aged 45. **Part affected** : Glands in neck. **Duration** : 5 years. **Physical condition** : Big, burly man. Has had very good health. **Cardiovascular condition** : The radial arteries are markedly thickened and tortuous. P. M. Old visceral plaque on pericardium over left ventricle. Advanced atheroma of aorta. Kidneys in a state of acute ascending nephritis. **Syphilis** denied, but Wassermann's reaction definitely positive. **Remarks** : Three children ; two of them were premature and died soon after birth. The case is referred to on p. 26.

Case 2. Male, aged 67. **Part affected** : Glands of neck. **Duration** : $\frac{7}{12}$ year. **Physical condition** : Heavy, powerful man. **Cardiovascular condition** : Heart and vessels apparently healthy. **Syphilis** forty-eight years ago. **Gout** : Several attacks of typical gout have laid him up for a fortnight at a time. Attacks precipitated by beer. **Remarks** : See Appendix C, No. 15.

Case 3. Male, aged 39. **Part affected** : Glands of neck. **Duration** : $\frac{5}{12}$ year. **Physical condition** : A stout, muscular, heavily built man of plethoric appearance. Is a drill sergeant and has served many years in army. **Cardiovascular condition** : Heart and blood-vessels apparently healthy. **Syphilis** in India eleven years ago. Treated for three months only. Wassermann positive. **Remarks** : Very heavy pipe smoker, getting through an ounce a day. Tongue clean and papillated. No pharyngeal lesion discernible.

Case 4. Male, aged 61. **Part affected** : Lower end of the oesophagus. **Duration** : 4 years. **Physical condition** : Big, strong man ; has been a sailor. **Cardiovascular condition** : Definite thickening and hardening of vessel all the way up the arm, and vessel visible pulsates and writhes throughout. P. M. Heart and valves healthy, very little atheroma of the aorta. Kidneys lobulated but structurally healthy. **Syphilis** : Forty years ago in Germany, when following the occupation of a sailor, had an attack of syphilis for which he was treated. His knee-jerks cannot be elicited. Slight Rombergism is present. The pupils are small but react to light. **Remarks** : Married many years, but wife has never been pregnant.

Case 5. Male, aged 67. **Part affected** : Lower end of the oesophagus. **Duration** : $\frac{4}{12}$ year. **Physical condition** : Very wasted when first seen. Has been accustomed to heavy work as gardener. **Cardiovascular condition** : Arteries thickened and can be traced all the way up the arm from wrist to axilla. Pulsation is very visible, and the vessels can be seen straightening themselves with each heart-beat. Pulse slightly irregular. P. M. Mitral valves sclerosed. Aorta shows a fair amount of atheroma. Kidneys arteriosclerotic and with fibrotic changes. **Syphilis** : Denies syphilis, admits gonorrhoea. Has been a very heavy and habitual drinker. P. M. Was found a general chronic peritonitis with intestines matted together. **Remarks** : Several children and no history of miscarriages.

Case 6. Male, aged 48. **Part affected** : Skin in parotid region. **Duration** : $\frac{2}{12}$ year. **Physical condition** : Strong, muscular man. Is a police-constable. **Cardiovascular condition** : Vessels good. Heart enlarged. P.M. Heart slightly hypertrophied. Cardiac muscle and valves healthy. Some patchy atheroma, especially in abdominal aorta. Kidneys show scarring and patchy arteriosclerotic change. **Syphilis** : Thirty years ago had an attack of syphilis diagnosed by medical man. **Remarks** : Wife insane ; had no miscarriages.

Case 7. Male, aged 45. **Part affected**: Side of the neck. **Duration**: $\frac{9}{12}$ year. **Physical condition**: Well-developed, strong, and muscular man. A blacksmith. Has had excellent health. **Cardiovascular condition**: Some thickening of peripheral arteries. P. M. Heart hypertrophied. The aort somewhat atheromatous, the lungs emphysematous, and the kidneys show slight interstitial nephritis. **Syphilis**: Venereal sore 2 years ago which has left well-marked scar. Wassermann negative.

Case 8. Male, aged 6 **Part affected**: The inner canthus of the left eye. **Physical condition**: Well-nourished, powerful, muscular man. A miner. **Cardiovascular condition**: Extreme thickening and tortuosity of peripheral vessels. **Syphilis**: Much scarring following an attack 40 years ago. There has been laryngeal trouble and the voice is almost gone. A tracheotomy has been necessary owing to tracheal stenosis. **Remarks**: Separated from wife.

Case 9. Male, aged 43. **Part affected**: Sigmoid colon. **Duration**: 2 years. **Physical condition**: Highly-coloured, healthy-looking man. 'Never been laid up in my life.' A butcher. **Cardiovascular condition**: Radial vessel thickened. Pulse wave large. Soft systolic murmur over praecordium. Systolic pressure 104. Diastolic pressure 84. **Syphilis**: He had a venereal sore twenty years ago and the doctors differed as to whether it was syphilis or no. **Remarks**: Seven children, no miscarriages.

Case 10. Male, aged 40. **Part affected**: Rectum. **Duration**: $1\frac{3}{12}$ years. **Physical condition**: Stout, heavily-built, high-coloured man. Muscular. Has been a sailor. **Cardiovascular condition**: Fairly good. **Syphilis**: A chancre sixteen years ago and a scar now present. Definite tabetic signs. Knee-jerks absent. Paraesthesia in legs. Unequal and contracted pupils and the Argyll Robertson syndrome. **Remarks**: Wife has had several miscarriages.

Case 11. Male, aged 51. **Part affected**: Rectum. **Duration**: $\frac{2}{12}$ (?) years. **Physical condition**: Muscular and high coloured. Has been in the navy. **Cardiovascular condition**: Artery walls very much thickened and tortuous. **Syphilis** thirty-two years ago with rash and much scarring. Leucoplakia of tongue. **Remarks**: Wife has borne healthy children and no miscarriages. Rectum in Museum of Cancer Hospital, New Series, No. 573.

Case 12. Male, aged 59. **Part affected**: Rectum. **Duration**: $\frac{6}{12}$ year. **Physical condition**: Medium build, fairly well developed. **Cardiovascular condition**: Arteries throughout upper arm are considerably thickened. Heart in good condition. The aortic second sound is accentuated. **Syphilis** thirty-nine years ago, diagnosed by a distinguished surgeon. **Gout**: Has had many minor though definite attacks of gout, affecting chiefly the feet and laying him up for a few days at a time. A medical man writes that he has treated him in several of these attacks. **Remarks**: Patient's brother, who fell ill about same time as patient, died, and at P. M. was found to be suffering from a carcinoma of the lower end of the oesophagus. See Appendix C, No. 8.

Case 13. Male, aged 55. **Part affected**: Caecum. **Duration**: $\frac{3}{12}$ year. **Physical condition**: Fair. Has had very good health. Is a house painter. **Cardiovascular condition**: Good. **Syphilis** twenty-five years ago with well-marked rash. **Remarks**: Wife suffering from syphilitic (?) stricture of rectum. One miscarriage and four healthy children.

Case 14. Male, aged 84. **Part affected**: Skin of forehead. **Duration**: 1 year. **Physical conditions**: Fine, sturdy old man. Heavily built and muscular, and still strong and active. Has been in army and afterwards warder in a convict prison. **Cardiovascular condition**: Radial vessel large, with big wave. Vessel wall thickened but not very markedly so, considering patient's advanced age. The cardiac sounds are very faint. There is a soft systolic murmur audible all over praecordium. **Syphilis**: Severe attack of syphilis fifty-seven years ago. Treated and no reminders since. **Remarks**: Wife has had no miscarriages and has borne six healthy children.

Case 15. Female, aged 43. **Part affected**: Cervix uteri. **Physical condition**: Poor physique. **Cardiovascular condition**: Good. **Syphilis**: Congenital syphilis. **Remarks**: Eight miscarriages.

Case 16. Female, aged 29. **Part affected**: Cervix uteri. **Physical condition**: Poor physique. **Cardiovascular condition**: Good. P. M. Granulations on mitral valves. Arteries healthy. Kidneys showed active chronic interstitial nephritis. **Syphilis**: Congenital syphilis. **Remarks**: One miscarriage.

Case 17. Female, aged 47. **Part affected**: Cervix uteri. **Duration**: 1 year. **Physical condition**: Poor physique. Signs of early rickets. **Cardiovascular condition**: Good. **Syphilis** doubtful. **Rheumatism**: 'Rheumatic fever' six years ago. **Remarks**: Three miscarriages, five living children, all died before 5 years of age. Several wasted from birth. Husband in army.

Case 18. Female, aged 69. **Part affected**: Cervix uteri. **Duration**: 2 years. **Cardiovascular condition**: A little arteriosclerosis. **Syphilis** (?): Two living children and four miscarriages. The history of the pregnancies shows progressive prolongation of the period of gestation till viable children were reached.

Case 19. Female, aged 31. **Part affected**: Cervix uteri. **Duration**: $\frac{6}{12}$ year. **Physical condition**: Large, stout subject. **Cardiovascular condition**: Heart and vessels healthy both clinically and P.M. Kidneys disorganized. **Syphilis** probable. Nine pregnancies and two children born alive. History of pregnancies as for case 18. Husband in navy.

Case 20. Female, aged 43. **Part affected**: Breast. **Duration**: $1\frac{6}{12}$ years. **Physical condition**: Medium build. **Cardiovascular condition**: Heart and vessels apparently healthy. **Syphilis** (?): Four miscarriages and five children, of whom two lived only a few hours and the third only a few weeks.

Case 21. Female, aged 58 years. **Part affected**: Breast. **Duration**: 6 years. **Physical condition**: Spare, slight woman. **Cardiovascular condition**: Definite thickening of peripheral vessels of a pathological degree. Heart sounds loud and wave large. A systolic murmur present in aortic area. **Syphilis** (?): Two miscarriages, four still-born children, six children born alive none of whom lived more than five years and several of whom had snuffles. Husband in army.

Case 22. Female, aged 60. **Part affected**: Breast. **Duration**: $\frac{1}{12}$ year. **Physical condition**: Medium build. **Cardiovascular condition**: Heart and vessels apparently healthy. **Syphilis**: Definite history of syphilis. Had an illegitimate premature child when 18 years of age. **Remarks**: Is a typical tabetic. Suffers with lightning pains and gastric crises. Knee-jerks absent and anaesthetic areas present. Well-marked Rombergism. Argyll Robertson syndrome present, but imperfect.

Case 23. Male, aged 58. **Part affected**: Prostate. **Physical condition**: Largely built, powerful man. Has been in army. **Cardiovascular condition**: Heart and vessels apparently healthy. Patient is hemiplegic. **Syphilis**: Definite syphilis forty-two years ago. Well treated. **Remarks**: Attack of hemiplegia a year before onset of bladder symptoms. Seen at the time by a neurologist and pronounced to be suffering from a cerebral haemorrhage.

Appendix C.

Non-oral Cases with History or Signs of Gout.

Case 1. Male, aged 61. **Disease**: Rodent ulcer of cheek. **Physical condition**: Fairly good. **Cardiovascular condition**: Pulse 64, irregular in force and frequency. Much degeneration of peripheral vessels, which are thick, hard, tortuous, and nodular. **Gout**: Many attacks, chiefly in arms, hands, and legs. Numerous tophi in ears. Dupuytren's contracture. Attacks of gout commenced when about 40 years old.

Case 2. Male, aged 69. **Disease**: Carcinoma of skin of neck. **Duration**: $\frac{5}{12}$ year. **Physical condition**: Well nourished and preserved. Excellent health. **Cardiovascular condition**: Much thickening and tortuosity of peripheral vessels. Heart good. Emphysema. **Gout**: Has clearly suffered with gout, and has had several attacks in big toes and in backs of hands.

Case 3. Male, aged 52. **Disease**: Rodent ulcer of cheek. **Duration**: 2 years. **Physical condition**: Weathered, red-faced appearance. A powerfully-built man looking less than his age. A painter. **Cardiovascular condition**: Great thickening of radial vessels. Accentuation of aortic second sound. Emphysema. **Gout**: Several attacks of gout beginning in big toe.

Case 4. Male, aged 74. **Disease**: Rodent ulcer of face. **Duration**: 5 years. **Physical condition**: Red-faced muscular man. A labourer. **Cardiovascular condition**:

Pulse 62. Much thickening of vessels. Emphysema. **Gout**: Has had a series of attacks of rheumatic pain in legs. Never in big toes. There is a whole series of tophi (?) in the ears.

Case 5. Male, aged 48. **Disease**: Endothelioma of cheek. **Duration**: 2 years. **Physical condition**: Big, strong, John-Bull-like fellow. Good health except for gout. Railway clerk. **Cardiovascular condition**: Radial artery a little tortuous and nodular. **Gout**: Has been for the last sixteen years subject to attacks of acute gout. The attacks begin in the feet, and sometimes affect hands and knees. There are well-marked tophaceous changes in the big toe and in both ears. Last year suffered with an attack of 'enlargement of liver' (said by doctor to be due to beer), and he had an attack of gout with this. As soon as he came into hospital he developed an extremely severe attack of gout, which I was able to watch, and which was typical in all respects. Later he developed a milder attack, which I also observed. He used to be a porter, but ten years ago he was put on office work and the gout has since been worse. **Remarks**: Tumour of cheek in Museum of Cancer Hospital, New Series, No. 536.

Case 6. Male, aged 77. **Disease**: Rodent ulcer of face. **Duration**: 6 years. **Physical condition**: Muscular, active man, looking less than his age. Has been in army, and since then a dock labourer. **Cardiovascular condition**: The pulse is trigeminal. Artery walls very markedly thickened and tortuous. Cardiac sounds exceedingly faint. **Gout**: Has suffered from occasional attacks of gout for years, and one of these, affecting the right hand, occurred while under observation in hospital. This attack affected chiefly one hand, and two of the fingers became swollen and puffy. Previous attacks involved the big toe.

Case 7. Male, aged 66. **Part affected**: Lower end of oesophagus. **Duration**: $1\frac{6}{12}$ year. **Physical condition**: Very emaciated. Brewer's labourer. **Cardiovascular condition**: Extreme thickening and hardening of radial vessels. Cardiac sounds very faint. P. M. Heart muscles and valves good. In the descending aorta there was a little fatty degeneration of the intima, and in the arch there was more advanced atheroma. The coronary arteries were extensively diseased, showing well-marked calcareous degeneration, but the calibre of the vessels was not much diminished. Kidneys small and typically arteriosclerotic. **Gout**: Has had numerous attacks of gout. which have laid him up for a few days up to (on one occasion) as long as a month. Tophi in both ears. Dupuytren's contracture of both hands. Attacks usually begin in the feet and extend afterwards to the hands, but of late years there has been a tendency for the hands to be affected more than the feet.

Case 8. Male, aged 59. **Part affected**: Rectum. **Duration**: $1\frac{6}{12}$ year. **Physical condition**: Medium build, fairly well developed. **Cardiovascular condition**: Arteries throughout upper arm considerably thickened. Heart in good condition. **Syphilis** thirty-nine years ago, diagnosed by a distinguished surgeon. **Gout**: Has had many minor though definite attacks of gout, affecting chiefly the feet and laying him up for a few days at a time. A medical man writes that he has treated him in several of these attacks. **Remarks**: Patient's brother, who fell ill at about the same time as patient, died, and at P. M. was found to be suffering from a carcinoma of lower end of oesophagus. See Appendix B, No. 12.

Case 9. Male, aged 58. **Disease**: Carcinoma of rectum. **Duration**: $1\frac{3}{12}$ year. **Physical condition**: Muscular, weather-beaten man. Good health, except for gout. Has been a coachman, but had to give up because he was repeatedly disabled by gout. Well-marked arcus senilis. **Cardiovascular condition**: Arteries throughout upper limbs greatly thickened and tortuous. Heart sounds faint. Congested ring of vessels round chest at line of attachment of diaphragm. Average systolic pressure 140 mm. Average diastolic pressure 100 mm. **Gout**: Has constantly had to lie up with gout, the attacks lasting 6–7 weeks, and sometimes longer. First symptoms of rectal trouble came on during an attack of gout. There are well-marked tophi in both ears. Metatarso-phalangeal joints of both great toes show old inflammatory changes, and on right side the pointing of a tophaceous nodule. Dupuytren's contracture of both hands. A doctor who had attended him for twenty years writes : ' I believe he used to drink much more than he ought.... His attacks of gout were subacute and did not get well readily.... His feet, wrists, and knee-joints were affected.' The patient's father suffered all his life from gout. **Remarks**: Rectum in Museum of Cancer Hospital, New Series, No. 505.

Case 10. Male, aged 53. **Disease**: Carcinoma of rectum. **Duration**: 1 year. **Physical condition**: Strong, well-built man. Has done a good deal of painting and has

suffered with painter's colic. Very well marked arcus senilis. **Cardiovascular condition**: Arteries large, thickened, tortuous, and nodular. A soft systolic murmur at aortic cartilage and accentuated second sound. Systolic pressure 174 mm. Diastolic pressure 130 mm. **Gout**: Often been laid up with attacks of gout, during which 'the feet swell and there is burning pain in the joints of the big toe'.

Case 11. Male, aged 32. **Disease**: Carcinoma of rectum. **Duration**: 2 years. **Physical condition**: Fairly muscular. **Cardiovascular condition**: Thick, tortuous peripheral vessels. **Gout**: Laid up a couple of years ago for some weeks with pain and swelling in feet and legs. There are apparently tophi in the ears. The attack was not typical of gout and did not commence in the great toe.

Case 12. Male, aged 53. **Disease**: Carcinoma of ascending colon. **Duration**: $\frac{1}{12}$ year. **Physical condition**: Powerfully built, high coloured, sturdy man. **Cardiovascular condition**: Radial vessels very large and somewhat thickened and tortuous. Systolic pressure 129 mm. Diastolic pressure 101 mm. Gout was diagnosed by a doctor eighteen months ago, when patient had swelling of hands, &c. The attack, however, was not typical.

Case 13. Female, aged 63. **Disease**: Carcinoma of left breast. **Duration**: 4 years. **Physical condition**: Very high colour. Plethoric type. **Cardiovascular condition**: Distinct thickening of radial vessels. Second sound accentuated at base. **Gout**: Has suffered a good deal with typical attacks of gout in big toes and hands and elbows. Tophi in ears.

Case 14. Female, aged 70. **Disease**: Carcinoma of left breast. **Physical condition**: Very high colour. Congested face. Stout. **Cardiovascular condition**: Much thickening and tortuosity of peripheral vessels. **Gout**: Attended the out-patient department of a hospital for years together with her sister. Both of them suffering with extremely advanced severe and intractable tophaceous gout. One day in examining the patient's chest a tumour was found in the breast. The organ was amputated and the tumour found to be carcinoma on microscopic examination.

Case 15. Male, aged 67. **Part affected**: Glands of neck. **Duration**: $\frac{1}{12}$ year. **Physical condition**: Heavy, powerful man. **Cardiovascular condition**: Heart and vessels apparently healthy. **Syphilis** forty-eight years ago. **Gout**: Several attacks of typical gout have laid him up for a fortnight at a time; attacks precipitated by beer. **Remarks**: See Appendix B, No. 2.

LYMPHADENOMA WITH RELAPSING PYREXIA [1]

By ARTHUR SALUSBURY MAC NALTY

With Plates 5–7

THE arguments that this thesis will endeavour to maintain are as follows: 1. That there is a definite type of lymphadenoma associated with relapsing pyrexia. 2. That certain cases of tuberculous adenitis and of chronic pulmonary tuberculosis with relapsing pyrexia bear a close resemblance to this variety of lymphadenoma, and in many instances are only distinguishable by post-mortem observation.

History. In 1832, in his paper on 'Some Morbid Occurrences of the Glands and Spleen', in Case 7, Hodgkin gives an account of a female, aged 25, who, while under observation, had two attacks of intermittent pyrexia. At the post-mortem, deposits were found in the spleen and the kidney. In all probability this was a case of relapsing fever in lymphadenoma without enlargement of the external glands. Twenty-six years later Wunderlich reported a case in which there were periodic rises of temperature and the lymphatic glands and spleen were enlarged. On one occasion he noted the fact that an increase in the size of the glands and of the spleen was concomitant with the rise of temperature.

In 1870 Murchison reported the case of a girl, aged 6 years, with enlargement and tenderness of the superficial glands of the body (cervical, axillary, and inguinal), dullness over the sternum (indicative of enlargement of the mediastinal glands), enlarged and tender spleen, and enlargement of the liver. The patient had periodic outbursts of pyrexia, and during the febrile periods both the cervical and the mediastinal glands increased in size, the latter fact being deduced from the increased area of dullness over the sternum. The duration of the whole illness was $2\frac{1}{2}$ years.

In 1873, in the course of a discussion at the Pathological Society on a case of leucocythaemia shown by F. Taylor, William Jenner 'remarked upon the occurrence of pyrexia in allied cases, and upon the fact that exacerbations of pyrexia coincided with increase in the size of the glands, and falls of temperature with subsidence of the glands'.

William Gowers, in 1879, considerably augmented our knowledge of the subject in a comprehensive article in Reynolds's *System of Medicine*, based on one hundred

and fourteen recorded cases. In forty of these cases, in which particular attention was paid to the question of pyrexia in lymphadenoma, he found that in thirteen pyrexia was absent or only present as the expression of some intercurrent malady; in the remaining twenty-seven cases pyrexia was present and bore an intimate relation to the disease. He states that the pyrexia in lymphadenoma is variable and irregular, that it is commoner in subjects under twenty years of age, and that the following three types may be recognized : 1. A continuously raised temperature with slight diurnal variations of a degree or a degree and a half. 2. Periods of pyrexia in which for several days a high temperature is maintained, the daily variation being slight. Alternating with these pyrexial periods are intervals of several days in which the temperature is normal or nearly so. 3. A pyrexia characterized by morning remissions, the temperature being always higher in the evening than in the morning; the diurnal variations are from one to three degrees.

Gowers adds that mixed varieties of these three types may occur, that pyrexia to a greater or less degree appears to be a characteristic of the disease even in its earlier stages, and alludes in the course of the article to a case under the care of Wilson-Fox at University College Hospital, which resembled that of Murchison in that there was intermittent pyrexia and during the pyrexial period the glandular enlargement was much more pronounced. The case is in all probability the one that he communicated to the Clinical Society in 1876 under the title 'A Case of Lymphatic Leucocythaemia treated with Phosphorus'.

In 1885 especial attention was paid to this subject by Osler, who, in Pepper's *System of Medicine*, in the article on Lymphadenoma, referred to a case in which, at intervals, a high grade of pyrexia occurred. Associated with the increased temperature were paroxysms of the malarial type, with rigors and hot and sweating stages. The glands visibly increased in size and diminished in the apyrexial intervals. In the same year in which Osler's article appeared, Pel recorded in the *Berliner klinische Wochenschrift* a case which he described as an infectious form of 'pseudo-leukaemia'. It was an acute malady of about five months' duration; the subject was a male of twenty-five years of age. Periodic rises of temperature were noticed, in which the spleen became enlarged; there was no enlargement of the superficial glands throughout the disease. Like Hodgkin's early example the case was presumably lymphadenoma, for Pel in 1887 recorded two further cases, in one of which there was enlargement of the supraclavicular and inguinal glands, while he groups all three cases under the one heading. In the same category must be placed the disease described by Ebstein in 1887 as 'das chronische Rückfallsfieber, eine neue Infectionskrankheit', and Renver's case of 'lymphosarcoma with recurrent fever' (1888).

In the meantime additional cases of relapsing fever with glandular enlargement had been reported by Kast, Hanser (who described his case as confirming the observations of Ebstein), and Klein. In 1892 Dreschfeld of Manchester, in a clinical lecture, reviewed the subject of acute Hodgkin's disease. He quoted in detail three cases, all of which terminated fatally, with an average duration

of six weeks' illness. He obtained autopsies. In all three cases pyrexia was present, and in two of the cases there was no enlargement of the superficial glands. The duration of the illness after admission to hospital was short; the first case lived for eight days, the second for six days, the third for seven days. All the cases may be regarded as examples of lymphadenoma with relapsing pyrexia which came under observation in the terminal stage of the disease.

Dreschfeld concludes :—' One may classify acute Hodgkin's disease or acute pseudo-leucocythaemia into various types, corresponding to the types of chronic Hodgkin's disease, namely, one type in which the superficial glands are enlarged, of which the third case is a good example ; a second type in which the intrathoracic glands are prominently affected, the superficial glands showing no change—this type is well illustrated by the first case ; and a third type where the prominent symptoms refer to an affection of the abdominal organs and intra-abdominal lymphatic glands, and which is illustrated by the second case.' With regard to Dreschfeld's second and third types it must be admitted that the clinical distinction is a somewhat subtle one, and that in the majority of instances they dovetail into one another ; indeed, he himself goes on to say that the affection in all three types must be looked upon as a general one.

Dreschfeld pointed out that pyrexia was common to all cases of acute Hodgkin's disease and that it might have the hectic type or ' the somewhat characteristic chronic type of Gowers and Ebstein, that is, periods of pyrexia alternating with apyrexial periods '.

From 1892 to 1904 we are indebted to the investigations of Fischer, Westphal, Hohenemser, Finlayson, and Batty Shaw for further cases of lymphadenoma with recurrent pyrexia, while reference must be also made to Musser's article, ' Notes on the Fever of Hodgkin's disease,' which is discussed more fully in a later section of this thesis.

Batty Shaw's case is an example of a special type. It was that of a man admitted to hospital with a mass of enlarged glands on the left side of the neck, lying underneath and on either side of the sterno-mastoid muscle and reaching from the ear to the clavicle. One or two glands near the clavicle showed some tenderness, were softer than the others, and the skin in the neighbourhood was distinctly red. Shortly after admission the temperature rose to 102°, the girth of the neck increased, and the tenderness of the glandular swellings was intensified. A number of glands were removed and the patient discharged. Two months later the patient was readmitted. In the interval he had had seven attacks of fever with shivering, vomiting, and diarrhoea. The glands had greatly enlarged in the febrile period and had shrunk to a small size in the intervals of apyrexia. The spleen had now enlarged. It was observed in the course of two pyrexial intervals in hospital, that there was a measurable increase in the girth of the neck ; ' in the latter attack the upper part of the glandular mass had become much softer and smaller, the lower part larger and very much more tender, the skin over it becoming quite purplish in colour and

appreciably warmer to the hand than the surrounding part.' Further relapsing pyrexia occurred and eventually the patient died, shortly after a febrile period. Post mortem the cervical axillary, mediastinal, and retroperitoneal glands were lymphadenomatous : the spleen was enlarged and contained ' hard-bake ' deposits.

In 1904 Frederick Taylor published a paper on 'The Chronic Relapsing Pyrexia of Hodgkin's Disease ', with illustrative cases. Taylor's contribution to the subject is a valuable one : he draws attention to the fact that cases of relapsing pyrexia occur in Hodgkin's disease both with and without enlargement of the external glands, his authority for this statement being principally based upon the cases of Pel, Ebstein, Hanser, and Volckers ; he states that ' on the one hand, I have reason to believe that the profession is not widely familiar even with the occurrence of this relapsing fever in Hodgkin's disease, much less with its extraordinary duration and persistence ; and, on the other hand, I wish to call attention to the great value which a knowledge of its characters may have for the diagnosis of such obscure cases as that which Ebstein recorded, and of some which I shall myself here record '.

Taylor affirms that of the different varieties of temperature noted in lymphadenoma (continuous, remittent, intermittent, and relapsing) the relapsing type is the most rare, but if present is the most characteristic ; he lays stress upon the circumstance that from the charts, both of his own cases and of those communicated by Ebstein and Pel, it is possible to affirm that the relapsing form of pyrexia terminates always by lysis, even if somewhat rapidly, and the acme is removed by three or four days from the first subnormal temperature of the interval. Three cases are adduced in detail in the course of the paper. Special attention was paid to the pyrexia and careful analyses of its phases in each case are submitted. All three cases terminated fatally, but unfortunately postmortems were not available.

The first case was one of relapsing pyrexia with enlargement of the cervical glands ; a small gland was present in the axilla. It is not stated that the glands increased in size during the pyrexial period. The glands were removed by operation and were stated to be lymphadenomatous.

In the second case there was also enlargement of the cervical glands ; these were removed by Symonds ; microscopically they showed simple hyperplasia. The patient was readmitted to hospital a few months later for a large movable mass in the abdomen ; intermittent pyrexia was present.

The third case showed enlargement of the cervical glands and, on occasions, of the superficial glands in the axilla and groin. The enlargement was, however, slight and variable. A complete and continuous record of the temperature was kept for twelve months and six days ; it terminated four and a half months before death. The record shows that the variations in the pyrexial process were somewhat complex. As in the first two cases, there were alternations of periods of pyrexia with periods of apyrexia, but long periods also occurred in which fever was observed every day, and this fever was subject to exacerbations in which periods of relatively high fever alternated with periods of relatively low fever.

Taylor concludes his paper with the following statements: ' A varying temperature is common in lymphadenoma; that varying definite recurrences occur in some cases, the recurrences alternating with periods of complete apyrexia ; that the temperature may be continuously high for long periods, and that periods of higher fever may then alternate with periods of lower fever; that the recognition of the relapsing form of pyrexia may be of great assistance in the diagnosis of some doubtful cases.'

It is clear from this summary of the history of the subject that the question of relapsing fever in lymphadenoma has already engaged the attention of several investigators, notably Gowers, Musser, and Taylor.

When these researches were carried out the work, of necessity, had to be pursued on clinical lines alone, for at that time lymphadenoma existed as a clinical and not as a pathological entity.   These are the days when the pathologist is abroad in the land, and clinical results may be subjected to the criticism that they are unsupported by pathological evidence.

It has been shown by the work of Andrewes, and especially by that of D. M. Reed, working in the Johns Hopkins Hospital in 1902, that lymphadenoma presents a characteristic histological picture, distinguishable from the pathological conditions brought about by other diseases, so that if tuberculosis occurs as a secondary infection in a gland previously affected with lymphadenoma the two processes can be differentiated.

According to Reed, the microscopic appearance of a lymphadenomatous gland is as follows: 1. There is an overgrowth of the reticulum ; the lymphocytes are less numerous, and there is a proliferation of the endothelial cells. 2. Some of the endothelial cells are enlarged and constitute the characteristic ' lymphadenoma cells ' which were first described by Virchow.   They contain a few centrally placed, deeply staining nuclei, and are smaller and rounder than the 'giant cells' of tuberculosis; they often show mitosis. 3. There is great proliferation of the connective tissue leading to fibrosis ; if this factor predominates the glands are hard ; if the lymphadenoma cells are in excess the glands are soft.   4. Eosinophil cells are present and sometimes form a marked feature in the gland section.   These changes occur uniformly throughout the gland, no trace of the original structure being left.

T. Longcope, in his admirable monograph, ' The Pathological Histology of Hodgkin's Disease,' published in the Bulletin of the Ayer Clinical Laboratory of the Pennsylvania Hospital in 1903, confirmed D. M. Reed's work, but adopted a somewhat different classification of the histological changes.

An Account of the Disease.

Introduction.   An attempt is made in the following section to construct a brief description of lymphadenoma with recurrent pyrexia, based upon the results of the investigations carried out upon five cases here reported, and upon twenty-seven cases collected from the literature.   An analysis of the salient features of these thirty-two cases is appended.

TABLE A.—*Lymphadenoma with Recurrent Pyrexia with Enlargement of the Superficial Glands.*

Case 1 (Wunderlich). **Enlargement** of superficial glands, spleen. Pyrexia with swelling of glands noted once.

Case 2 (Murchison). F., aged 6. **Enlargement** of axillary and inguinal (tender), mediastinal glands, spleen, liver. Cervical and mediastinal glands enlarged with pyrexia. **Duration** 2½ years. Dilatation of heart with a pyrexial period. Post-mortem examination.

Case 3 (Gowers). M., aged 17. **Enlargement** of cervical, femoral, inguinal, mediastinal, prevertebral, lumbar, iliac glands, spleen, liver. Glands enlarged with pyrexia. **Duration** 10 months. Chill and cough at onset. Post-mortem examination. Mediastinal growth.

Case 4 (Osler). **Enlargement** of glands with pyrexia.

Case 5 (Pel). M., aged 41. **Enlargement** of supraclavicular and inguinal glands, spleen (periodic with pyrexia), liver. Glands enlarged with pyrexia. **Duration** 13–14 months.

Case 6 (Kast). M., aged 7. **Enlargement** of superficial glands, spleen, liver. Glands enlarged with pyrexia. **Duration** 5½ months.

Case 7 (Hanser). M., aged 25. **Enlargement** of superficial and deeper glands (? tumour in abdominal cavity), spleen, liver. **Duration** 1 year. Cardiac dilatation present, increased in pyrexial period. Anasarca 4 weeks before death.

Case 8 (Klein). F., aged 51. **Enlargement** of superficial glands, spleen, liver. Glands enlarged with pyrexia. **Duration** 13 weeks. Jaundice 5 years previously.

Case 9 (Fischer). M., aged 34. **Enlargement** of superficial and mediastinal glands. **Duration** 18 months. Dyspnoea present.

Case 10 (Westphal). M., aged 25. **Enlargement** of superficial glands, spleen, liver. **Duration** 1 year.

Case 11 (Hohenemser). M., aged 28. **Enlargement** of superficial and bronchial glands, spleen, liver. **Duration** 3½ months.

Case 12 (Finlayson). M., aged 39. **Enlargement** of superficial and deeper glands. **Duration** 1 year 5 months. Occasional epistaxis. All external glands, except those in the left groin, disappeared completely during the course of the disease. Great enlargement of mediastinal and abdominal glands. Post-mortem examination.

Case 13 (Batty Shaw). M., aged 41. **Enlargement** of superficial and mediastinal glands, spleen, liver. Glands enlarged with pyrexia (very marked). **Duration** about 8 months. Post-mortem examination. Glands red ; adherent to the skin.

Case 14 (Dreschfeld : Case III). M., aged 36. **Enlargement** of cervical and deeper glands. Glands enlarged with pyrexia. **Duration** 6 weeks. Very acute case; simulated glanders. Glands only noticed to be enlarged for a fortnight before death. Patient died in a febrile period. Post-mortem examination. Large mediastinal growth.

Case 15 (Dreschfeld). M. **Enlargement** of superficial and deeper glands (shown by sternal dullness and bronchial obstruction), spleen. Glands enlarged with pyrexia. **Duration** 2 months (recovery). Patient recovered under arsenic.

Case 16 (Taylor). M., aged 9. **Enlargement** of superficial and deeper glands, spleen, liver. Glands enlarged with pyrexia; painful. **Duration** 10 months. Pleural effusion (right side); pericardial effusion. Growths in lung and liver. Post-mortem examination.

Case 17 (Taylor). M., aged 41. **Enlargement** of superficial and deeper glands ; mass felt in right iliac fossa. Glands enlarged with pyrexia (not marked). **Duration** 10 months. Cervical glands enlarged for 3 years previously.

Case 18 (Taylor). F., aged 20. **Enlargement** of superficial and deeper glands ; mass felt in abdomen. Glands enlarged with pyrexia. **Duration** 3 years.

Case 19 (Taylor). M., aged 38. **Enlargement** of superficial glands, spleen, liver. Glands enlarged with pyrexia. **Duration** 4 years. Haematuria ; haematemesis ; pleural effusion. Disappearance of enlarged glands and appearance of other enlarged glands from time to time.

Case 20 (Musser). M., aged 16. **Enlargement** of superficial glands, spleen (tender). Glands enlarged with pyrexia. **Duration** 1 year. Systolic murmur at base of heart during pyrexial periods. Terminal icterus.

Case 21 (Ruffin). M., aged 24. **Enlargement** of superficial and deeper glands, spleen. Glands enlarged with pyrexia. **Duration** 1 year 2 months. Pigmentation of face and abdomen.

<div align="center">Cases reported in this Thesis.</div>

Case 22 (Case I). M., aged 23. **Enlargement** of superficial glands (? deeper glands), spleen. Glands greatly enlarged with pyrexia. **Duration** 1 year 3 months. Glands red and adherent to the skin.

Case 23 (Case II). M., aged 17. **Enlargement** of superficial glands (? deeper glands), spleen. Glands enlarged with pyrexia (slight). **Duration** of acute attack 6 weeks; patient still living. Cardiac murmurs. Disease simulated malignant endocarditis. Acute attack gave place to chronic lymphadenoma.

Case 24 (Case III). F., aged 8. **Enlargement** of superficial and deeper glands, spleen, liver. Glands enlarged with pyrexia. **Duration** 6 months to present time. Physical signs in the chest varying in the course of the disease.

TABLE B.—*Lymphadenoma with Recurrent Pyrexia without Enlargement of the Superficial Glands.*

Case 25 (Hodgkin, Case 7). F., aged 25. **Enlargement** of spleen. Post-mortem examination. Deposit in spleen and kidney.

Case 26 (Pel). M., aged 25. **Enlargement** of spleen (in pyrexial period), liver. **Duration** 4–5 months.

Case 27 (Ebstein). M., aged 19. **Enlargement** of deeper glands, spleen (in pyrexial period). **Duration** 15 months.

Case 28 (Renvers). M., aged 31. **Enlargement** of deeper glands (enlarged and palpable in left iliac fossa), spleen (in pyrexial period). **Duration** 14 months.

Case 29 (Dreschfeld). M., aged 23. **Enlargement** of mediastinal glands, spleen. **Duration** 5 weeks. Left pleural effusion. Post-mortem examination. Mediastinal growth (anterior mediastinum). Deposits in liver and kidneys. Leucocytosis ; delirium.

Case 30 (Dreschfeld). M., aged 48. **Enlargement** of mesenteric and bronchial glands, spleen, liver. **Duration** 7 weeks. Post-mortem examination. Deposits in liver. Haemorrhages from gums. Leucocytosis.

<div align="center">Cases reported in this Thesis.</div>

Case 31 (Case IV). M., aged 34. **Enlargement** of bronchial, superior and posterior mediastinal glands, mesenteric and lumbar glands, spleen. **Duration** 11 months. Post-mortem examination. Deposits in spleen. Delirium.

Case 32 (Case V). M., aged 21. **Enlargement** of spleen. **Duration** 10 months to present time. Three years previous to onset had enlarged glands in neck, which have now disappeared. Delirium.

As has been already remarked, definite pathological evidence is lacking that the cases reported in the literature as lymphadenoma were really examples of this disease. Such evidence has only been available in recent years through the researches of D. M. Reed. All the five cases communicated in this thesis, however, have been investigated from a pathological standpoint ; affected glands were examined in four cases during life, in one case after death, and their lymphadenomatous nature fully established.

Consequently, in the light of these results, it is permissible to hark back to the records, to examine them afresh and, noting how far their clinical features can be correlated with those present in these five cases, to verify the assumption

of Taylor, Dreschfeld, and others that they are types of the remarkable disease now under consideration. As an example of the method pursued let me instance Case IV.

Case **IV** is the only instance of the disease without enlargement of the superficial glands at any time that has been definitely proved to be lymphadenoma, yet it immediately falls into line with six similar cases in the literature grouped together in Table B, albeit that certain of the authors themselves failed to recognize the true nature of the malady that had come under their notice. As a consequence we find it described under such various titles as: 'Some Morbid Appearances of the Glands and Spleen' (Hodgkin); 'Pseudo-leukaemia (infectious form)' (Pel); 'Das chronische Rückfallsfieber, eine neue Infectionskrankheit' (Ebstein); and 'Lympho sarcoma with Recurrent Fever' (Renvers).

These results may be criticized from two points of view. On the one hand it may be urged that what some are pleased to term a variety of lymphadenoma is so rare that it constitutes merely an abnormality of the disease, and that it is a work of supererogation to elevate it to the dignity of a special type.

To this criticism the reply is given that the cases harmonize with one another so closely in the type of pyrexia, their clinical course, and other features, that one is unable to regard them as only a collection of departures from the normal, more especially as one's views are fortified by the similar opinions held by such authorities as Dreschfeld, Taylor, and others.

The second objection is that, even if the existence of this special type be granted, the number of cases is too few to permit of a definite account being given. It needs but a slight knowledge of the history of medicine to verify the statement that descriptions of rare diseases have been given on many fewer cases than the thirty-two examples dealt with in this thesis. Again, how frequently it happens that when once a disease is recognized and described examples multiply. The most notable instance of this in recent times is the Adam-Stokes syndrome (bradycardia with epileptiform or apoplectiform seizures). Five years ago it was an easy matter to exhaust the literature of reported cases on this subject; to-day, with the stimulus given to investigation by the anatomical researches of Kent, Tawara, and Keith, together with the polygraph work of J. Mackenzie and T. Lewis and the results obtained from electro-cardiograms, the task is too gigantic for one investigator to accomplish, and cases of the disease are reported daily, alike in this country, in America, and on the Continent.

I have endeavoured to lay stress on the circumstance that this special type of Hodgkin's disease may be easily confounded with tuberculosis. Murchison's case, the first example of the disease to be at all fully described, 'had been for several weeks in the Brompton Hospital for Consumption, and had been there treated with quinine, iron, and cod-liver oil.'

In the same hospital, in the course of one year, I myself have encountered no less than three cases of the disease, and I am confident that when once this special type is generally recognized it will prove to be less rare. With this

preface or apologia the description of lymphadenoma with recurrent pyrexia may now be entered upon.

Definition.   A special variety of lymphadenoma, characterized by recurrent pyrexia.

Etiology.   Like that of the chronic form of lymphadenoma the etiology of the special variety remains obscure.

In all my cases frequent films were made from the blood and examined for parasites, with negative results; splenic puncture on two occasions in Case V yielded no information.   Blood cultures from the cases remained sterile, while exhaustive examinations of the various body-secretions gave no information of aetiological value.

The most prevalent belief with regard to the etiology of a febrile disease, like the one under consideration, is that it is due to a bacillus or to one of the protozoa.   With regard to the bacteriological view, Delbet, in 1895, announced the discovery of a bacillus in lymphadenoma, which, on slender evidence, is asserted to have produced generalized disease in one dog inoculated with material derived from a lymphadenomatous gland.   Stengel, quoting Verdelli, stated that in twenty-nine cases of lymphadenoma with recurrent pyrexia organisms were found.   Fischer made bacteriological investigations on twelve cases.   Cultures from the diseased glands and animal inoculations were negative, but in one case organisms were found present in the blood during pyrexia and absent in apyrexia.   He suggested that the pyrexia of lymphadenoma had its origin in a secondary infection.   I have been unable to confirm these results, and would emphasize the negative results of blood-culture in my cases.

Batty Shaw holds the view that ' lymphadenoma with recurrent fever is not a special form of disease, (but) that such cases are due to a terminal infection occurring any time during the last year of life of some patients affected with lymphadenoma '.   This belief is not supported by the facts that Taylor had two cases with recurrent fever that lasted for three and four years respectively; that in many of the cases there is no preceding history of lymphadenoma and the disease begins acutely, and that Case II began acutely and has now merged into the chronic, afebrile form of the disease.

I have found no parasites in the blood to support the theory of protozoal infection or to confirm the work of White and Proescher.

The remarkable outbursts of pyrexia; the periodic swelling and enlargement of the lymphatic glands that occur in certain cases, and, by analogy, the temperature charts of relapsing fever and of malaria; the fact that irregular fever appears in cases of trypanosomiasis and is associated with enlargement of the spleen, glandular swellings, and an increased number of trypanosomes in the blood, argue strongly for a protozoal origin of the disease.   There is no definite time-relation, however, between the outbursts of pyrexia, and thus the pyrexial periods are unlikely to represent definite stages in the life-history of a parasite.

It is here shown that such relapsing pyrexia may occur in chronic

pulmonary tuberculosis. Periodic fever has been also described in cases of malignant disease of the liver and stomach, in the malarial form (so called) of malignant endocarditis, in pernicious anaemia, leukaemia, and other blood-diseases (Batty Shaw).

Some circumstances may be noted which may possibly have an indirect bearing on the causation of the disease.

Age. It occurs in adolescent subjects and in early middle age. The oldest case is that reported by Klein, a woman of 51 years ; the youngest, Murchison's case, a girl of 6 years.

Sex. It is much commoner in the male than in the female ; in the collected cases it has been described in twenty-five males and only in five females.

Trauma. In one of Taylor's cases the appearance of enlarged cervical glands is said to have followed a blow on the neck.

Local septic affections. One case supervened on an attack of otitis media ; in another case the disease became manifest after a tonsillar abscess (Taylor).

Chronic lymphadenoma. This, undoubtedly, may precede the onset of the acute form of the disease ; thus, in one of Taylor's cases and in Case V, the cervical glands were enlarged for three years previous to the onset of the pyrexia. The disease in such cases appears to bear the same relation to the chronic form of lymphadenoma as subacute Bright's disease does to chronic Bright's disease. It is well known that a subacute nephritis may be superimposed on chronic nephritis, and frequently with a fatal result.

Morbid anatomy. The pathological appearances are identical with those described for lymphadenoma in the textbooks.

Onset. The onset is generally insidious ; the early symptoms may suggest influenza or the first stages of pulmonary tuberculosis.

In Dreschfeld's first case the disease was ushered in by a persistent cough with some expectoration ; in another of his cases a groom was suddenly taken ill with discharge from the nose, cough, shortness of breath, and pain in the chest, and the condition was at first thought to be glanders. Most patients complain of colds and chills, of languid feelings and listlessness, of inability to perform their usual work without undue fatigue, of aching pains in the limbs and back, or merely of general malaise.

Lymphadenoma with relapsing pyrexia may be classified into two main forms :—

(*A*) A form in which the external lymphatic glands exhibit enlargement, with or without enlargement of the internal lymphatic glands.

(*B*) A form in which the internal lymphatic glands are alone affected. These forms comprise three distinct clinical types.

1. The first with enlargement of the external glands. The glands do not greatly enlarge. During the pyrexial periods they may be painful, soft, and tender, but they do not become attached to the skin, nor does the skin covering the glands become red and oedematous. The glands may remain of the same size during both the febrile and afebrile periods.

2. The second type is a very remarkable one and is exemplified in Batty Shaw's case and in Case I.

In the apyrexial stage the external glands may be small, freely movable, and free from attachment to one another or to the skin. With the onset of pyrexia the clinical picture changes with marvellous rapidity. The glands swell up and a single gland may reach the size of a cricket-ball; they are hot, painful, and tender to touch; they are, apparently, adherent to the skin, and the skin over them is red or purple and sometimes oedematous. They closely resemble suppurative glands on the point of discharging pus. Then, as lysis occurs, the glands shrink down to their original size, and the pain, tenderness, and heat are in abeyance until the process is repeated in the next pyrexial period.

There is no more wonderful sight in medicine than to see one of these tense, inflamed, prominent glands, which the surgical tyro would itch to attack with a scalpel, shrink down to the size of a pea, only to be detected by palpation.

3. The third type is that in which the internal glands alone are involved and only general symptoms are present.

Dullness over the sternum, palpation of the abdomen, or X-ray examination may possibly determine the presence of enlarged internal glands during life. Evidence of this nature is also adduced to show that in certain cases the internal glands enlarge. As already pointed out intermediate and mixed forms occur; in a case classified primarily as an example of the first clinical type the enlarged external glands may disappear, and the patient then present the features of an example of the third type, as happened in Case V.

Symptoms.

General. The patient may come complaining of general weakness, anaemia, or lassitude; in the obvious glandular types enlargement of the glands or their extraordinary periodic enlargement may cause him to seek advice. Frequent attacks of chills and colds with feverishness are present in the majority of cases. Haemorrhages, especially bleeding from the gums, occur. In cases of the third type enlarged intrathoracic glands will produce cough, dyspnoea, and evidence of venous obstruction. Excessive appetite appears to be a definite symptom; it was a marked feature during the apyrexial period in Case II and in Murchison's and Ebstein's cases, where it was characterized as enormous. Pel even went so far as to consider it a cause of the pyrexia.

The oedema observed in several of the cases may have a varied etiology. Thus it may be due to the enlarged glands pressing on the veins, the anaemic condition, or it may be a cachectic oedema and appear in the latter stages of the disease. All degrees of dropsy have been noticed, from a slight puffiness of the ankles to general anasarca.

The lymphatic glands. In the description of the external glandular types reference is made to the periodic enlargement of the glands in association with the febrile periods. The glands affected are tabulated in the analysis of cases;

the cervical groups of glands, both superficial and deep, appear to be most prominently affected, but as a rule all the other external glands (axillary, inguinal, and femoral) are also involved. The cervical glands may appear at first to be solely affected, and it is only later on in the disease that the other superficial glands become enlarged (see Case II and Musser's case). In the internal glandular type the mediastinal and mesenteric glands are most frequently lymphadenomatous. It may here be noted that, according to Ruffin, in the external glandular types the enlargement always begins in the glands of the neck and is usually unilateral.

The temperature. The temperature chart of this variety of lymphadenoma is perhaps the most conspicuous feature of this disease. In a typical case, following on a period of low pyrexia of normal or of subnormal temperature, there is a steady rise, occupying 2–4 days, to a maximum of 102°, 103°, 104°, or even 105° F. For about three days the temperature remains at a high level, and then there is a gradual fall by lysis which usually occupies about three days also. The temperature then becomes subnormal, at any rate for a few hours. During the pyrexial period, as a rule, the patient feels exceedingly ill; he has aching pains in the back and limbs, together with chills, profuse sweats, and loss of appetite. His expression is one of distress and anxiety.

In the external types the glands may become enlarged and painful as already described. The spleen may be greatly enlarged. Case II revealed the fact that enlarged glands may be recognizable for the first time in a pyrexial period. It should be noted that the diminution in size of the glands and spleen does not go strictly pari passu with the temperature; the relation is an approximate one, and their enlargement persists for a certain time of the early part of the afebrile period.

In the afebrile period the patient feels comparatively well, his appetite and spirits return, and he looks upon himself as on the high road to recovery, until the next pyrexial period dissipates the illusion.

The temperature between the periods of high pyrexia is often normal or subnormal, but alternations of periods of relatively high fever with periods of relatively low fever may occur. The duration, both of the pyrexial and of the apyrexial periods, is not a constant one, and they do not bear any relation to one another. This statement may be verified by a reference to the analysis of the temperature charts in my five cases.

The spleen. The spleen was enlarged in twenty-seven out of the thirty-two cases. The enlargement is more marked in the pyrexial period, and in four of the cases the fact is noted that the organ could only be felt below the costal margin at this period. Tenderness of the spleen is also associated with the temperature's periodicity. In Case II an attack of sudden and violent pain occurred in the region of the spleen, after which the organ became manifestly enlarged; this in all probability was due to infarction.

The liver. The liver was enlarged in many of the cases reported in the literature, the enlargement being presumably due to lymphadenomatous deposits in the organ. It was only enlarged in one of my cases (Case III).

The blood. Anaemia is a marked feature of the disease. It is progressive, as is shown by Case IV, where in the latter stages of the disease the red corpuscles dropped from 4,700,000 per cubic mm. to 2,788,000 per cubic mm. Further, the haemoglobin is reduced in amount, and vacuolation and poikilocystosis may occur. The leucocytes show no distinctive changes either as regards morphology or proportion. A polymorphonuclear leucocytosis was present in Dreschfeld's cases. A certain degree of eosinophilia may be present, but, as Dreschfeld and Kanthack pointed out in opposition to Ehrlich, it is of no diagnostic value.

The pulse shows no distinctive features in the apyrexial period. In the pyrexial period the pulse-rate varies directly with the height of the temperature.

The heart. Fatty degeneration may be present as a result of the anaemia. A certain degree of cardiac dilatation may exist. In one case (Murchison), while the patient was in the Brompton Hospital, it had been noted that the area of cardiac dullness was more extensive during the febrile paroxysms than in the intervals. Haemic murmurs may be heard, and their fleeting character, coupled with the high pyrexia, may lead to the erroneous diagnosis of malignant endocarditis. Case II is an admirable example of the presence of such murmurs in the disease. It is stated that enlarged glands in the neck, by pressure on the vagus, may produce cardiac irregularity.

The alimentary system. There is nothing distinctive in the alimentary system. Gastro-intestinal symptoms may declare themselves by vomiting and diarrhoea; on the other hand, obstinate constipation is sometimes caused by the pressure of enlarged intra-abdominal glands upon the intestine. In Case IV this was a very troublesome symptom.

The respiratory system. Cough, slight expectoration, and dyspnoea are frequently encountered. The shortness of breath may have its origin in the anaemia or be brought about by pressure of the enlarged glands. Lymphadenomatous deposits may be present in the lungs (Dreschfeld) and give rise to dullness, weak breath-sounds, and scattered crepitations. A remarkable circumstance is that this alteration in the pulmonary physical signs may be relapsing in character. Case III is a unique example of this feature of the disease.

The patient was under close observation in hospital for seven weeks. During this time the physical signs on the left side of the chest altered on no less than eight occasions. For a shorter or longer period there would be complete dullness, with weak breath-sounds, bronchial breathing, and scattered crepitations over the whole of the left lung, while compensatory exaggerated breath-sounds were present on the right side. Then, with surprising celerity, the abnormal signs would disappear, the left lung would become resonant to percussion and the breath-sounds normal and clearly audible.

The most probable explanation of this variability appears to be that the glands within the chest, like the external glands, were lymphadenomatous (definite mediastinal dullness was elicited, it should be noted); the glands enlarging in a pyrexial period occluded a bronchus and caused temporary

collapse of the left lung; in an afebrile period the glands diminished in size, the pressure was removed, and the lung returned to its normal condition. A reference to the case shows that this alteration in the pulmonary physical signs did not accurately follow the variation in the temperature. Like the enlargement and shrinkage of the glands themselves, the relation was an approximate one.

Pleurisy with effusion is a common complication. It cannot be regarded solely as a terminal infection, for it occurs in several cases during the course of the disease, notably in Ebstein's patient and in Taylor's third case. It is more frequently the result of pressure of enlarged glands upon the azygos or bronchial veins.

In Finlayson's case a nodule of old tubercle was found post mortem at the apex of the right lung, but in none of the cases under consideration did pulmonary tuberculosis occur as a complication. This is of interest when one reflects how frequently tuberculosis complicates the chronic form of lymphadenoma.

The question of the relation of tuberculosis to this special variety of lymphadenoma is dealt with in a subsequent section of the thesis. Bronchial catarrhs and bronchitis are not infrequent concomitants.

The skin. The anaemic condition gives rise to great pallor of the skin. In all my cases I observed that the skin assumed a peculiar icteroid or grey-yellow tint, and I find that Pel lays stress upon a similar appearance. True jaundice may ensue (Pel, Klein); it may be in its origin an obstructive jaundice caused by pressure of the enlarged glands upon the common bile-duct, as described by G. R. Murray. According to Musser, icterus is a usual terminal feature of the disease. Bronzing of the skin and pigmentation are noted in association with this acute variety of lymphadenoma. Skin-rashes were observed; in Case II an urticaria was present for a few days; in Taylor's third case a red patch appeared over the skin and simulated erythema nodosum, while an attack of chicken-pox, with suppurating vesicles, followed on the aspiration of a pleural effusion.

Subcutaneous purpuric haemorrhages may occur. Profuse sweats are usually associated with the close of a pyrexial period.

The nervous system. The pains that the patients complain of in the arms and legs may be due to the affected glands enlarging and pressing on the nerves. Inequality of the pupils is sometimes detected when the cervical sympathetic is involved. Retention of the urine is noted as a symptom. Very pronounced symptoms are seen on the mental side in certain of the cases. Such symptoms were a special feature of Case IV, where violent delirium, amounting almost to maniacal seizures, is described. The delirium cannot always be correlated with the pyrexia's height, for in the case to which reference has been already made the mental symptoms remarkably improved in the course of a pyrexial period. It may be mentioned that in Case V a sudden mental seizure occurred. The patient recovers marvellously quickly from such attacks of delirium or of mental irresponsibility.

Continuous delirium is common in the later stages of the disease.

The genito-urinary system. Lymphadenomatous deposits may occur in the kidneys. *The urine* is usually normal, but bile may be present, and occasionally a trace of albumin is detected. Haematuria was a prominent feature in one of the cases communicated by Taylor.

Course, duration, and termination. As a rule the disease is a progressive one; at first, a marked difference is noted in the general condition of the patient during the pyrexial and the apyrexial periods. With a febrile temperature all his symptoms are aggravated; headache, anorexia, general malaise, chills, and sweats make their appearance, and there may be delirium. In the afebrile stage these untoward symptoms disappear, the appetite returns, and he feels decidedly better. As however time elapses, this distinction in symptomatology, though always present, becomes much less marked. Under the strain of these bouts of pyrexia the patient's vitality flags; he grows weaker, there is a great emaciation, and the anaemia becomes extreme.

Type 1. *Enlargement of the Superficial Glands.*

2 cases 6 weeks, 1 case 2 months, 1 case 3 months 1 week, 1 case $3\frac{1}{2}$ months, 1 case $5\frac{1}{2}$ months, 3 cases 10 months, 3 cases 1 year, 1 case 13–14 months, 1 case 1 year 5 months, 1 case 1 year 6 months, 1 case $2\frac{1}{2}$ years, 1 case 3 years, 1 case 4 years.

Type 2. *Marked Enlargement with Softening of the Superficial Glands.*

1 case 8 months, 1 case 15 months.

Type 3. *Without Enlargement of the Superficial Glands.*

1 case 5 weeks, 1 case 7 weeks, 1 case 4–5 months, 1 case 10 months, 1 case 11 months, 1 case 14 months, 1 case 15 months.

It appears from the subjoined table that the shortest duration of any case was five weeks, and the longest four years; also, that the disease tends to run a longer course in cases with enlargement of the superficial glands than in those where the internal glands are alone involved. Death occurs in the majority of the cases. The process of devitalization continues and the patient eventually sinks into a state of coma. General anasarca, delirium, pleural effusion, and icterus are signs and symptoms that may immediately precede the terminal event.

I am only aware of two cases in which the acute condition appears to have subsided. Dreschfeld reported a case where a patient was admitted, suffering from intense anaemia, slight cough, and pyrexia. The patient had the usual symptoms of temporary enlargement of the glands (cervical and axillary), together with dyspnoea, dullness to the right of the sternum, signs of obstruction to the right bronchus, and enlargement of the spleen. Although the fact is not stated, it is probable that the pyrexia was recurrent in type (one period only being observed). The patient was given arsenic and recovered. The other case is

Case II in my series, which has now assumed the features of a chronic lymphadenoma.

Case V is still under observation, but shows no tendency to recovery.

The prognosis of the disease is therefore extremely unfavourable, and a shorter duration of life may be anticipated in the type where the intrathoracic and intra-abdominal glands are alone affected.

The Diagnosis.

The diagnosis of this variety of lymphadenoma is based upon—the relapsing character of the pyrexia ; the periodic enlargement of the lymphatic glands (external or internal); the periodic enlargement of the spleen ; the progressive anaemia and emaciation ; the characteristic grey-yellow tint of the skin.

It has been shown, in a consideration of the cases dealt with here, that the disease in its manifestations may closely or superficially resemble many other diseases. What diseases are simulated depends to a certain extent upon which of the two forms described is present, but not entirely, a notable exception being that of tuberculosis.

The differential diagnosis of some of these simulated diseases may now be discussed.

Relapsing fever. Lymphadenoma with recurrent pyrexia is distinguished from relapsing fever by the following points : (*a*) As Taylor has remarked, the pyrexial period terminates in relapsing fever by crisis and not by lysis. (*b*) In relapsing fever two attacks of recurrent pyrexia are the rule, a third is uncommon, and a fourth or fifth attack extremely rare. (*c*) The spirillum of Obermeier is present in the blood of patients with relapsing fever, and in this disease the agglutination test or Lowenthal's reaction may be obtained, the spirochaetes being clumped into non-motile masses.

Typhoid fever. Typhoid fever is distinguished by the presence of typhoid bacilli in the blood-cultures and by the Widal reaction.

Malignant endocarditis. This is simulated by the disease, and the mimicry is more intense when fleeting cardiac murmurs, due to temporary dilatation of the heart during a pyrexial period or of haemic origin, form a feature of the case (Case II). The negative results of blood-cultures, and the realization of the possibility of the error being made, are points to be relied on.

Animal parasites. Animal parasites, such as the *Ankylostomum duodenale,* will cause anaemia and paroxysms of pyrexia. This belief may be fostered by the presence of eosinophils in the blood in certain cases. It is overthrown, however, by the negative results of a search for the parasite.

Diseases of the blood. Spleno-medullary and lymphatic leukaemia have to be taken into consideration in view of the anaemia, the enlargement of the spleen, and the acute cases with enlargement of the external glands and haemorrhages. An examination of the blood will decide this question and also the doubt that

exists in other cases, where a diagnosis of pernicious anaemia, or of trypanoso-
miasis, or of malaria, has been hazarded. The diagnosis may have to be made
from glanders (Dreschfeld).

Acute adenitis. This may cause a certain amount of difficulty, especially
in the second type of case. The periodicity of the pyrexia and enlargement of
the spleen, if present, together with the associated symptoms and the absence of
suppuration, differentiate this variety of lymphadenoma from adenitis. In the
latter disease the glands affected will be in contiguity, and the enlargement will
not be general, as may be the case in the former affection.

From observations on my own cases, I cannot agree with G. R. Murray's
observation that the enlargement of the glands in lymphadenoma is invariably
painless. Gowers pointed out, long ago, that 'occasionally, when there is sudden
swelling of the glands from time to time, the rapid enlargement may be attended
with considerable pain'.

Sarcoma. Recurrent fever may occur in cases of sarcoma of the lymphatic
glands. It was present—(1) In a case described by Hammer in 1894, where the
patient for nine months had recurrent fever, the periods of pyrexia lasting from
one to six days, and the periods of apyrexia from one to twelve days. Pains
were complained of in the knees, and, at a later period, in all the bones of the
body, especially in the spine. Death occurred in nineteen months after the
onset of symptoms. Post mortem, the lymphatic glands were invaded by a round-
celled sarcoma, and nodules of similar growth were found on the serous mem-
branes. Numerous sarcomatous tumours were present in the bones. (2) In
Volcker's case, where the periods of pyrexia lasted fourteen days, and terminated
by lysis; the afebrile periods extended over seven to eight days; during the in-
tervals the temperature was never subnormal. A tumour was recognized situated
to the left of the vertebral column and extending from the umbilicus into the
pelvic cavity. Post mortem, it was found to be attached to the periosteum of
the lumbar vertebrae, while the retroperitoneal glands were enlarged; both they
and the tumour were sarcomatous. (3) In Seebohn's case, where recurrent
pyrexia was associated with a lymphosarcoma of the thymus, which involved
the neighbouring lymphatic glands. (4) In the case of Puritz, where the axillary
and left cervical glands were sarcomatous.

In sarcoma the fixation and hardness of the glandular swellings, their involve-
ment of neighbouring structures, their limitation and the discovery of primary
or secondary deposits elsewhere in the body, help to elucidate the problem. In
doubtful cases it may be permissible to remove a gland for diagnosis.

Tuberculosis. Lymphadenoma, with relapsing pyrexia, is exceedingly prone
to be confounded with some form of tuberculosis, and this must be considered
the most difficult disease to exclude in the differential diagnosis. A section of
the thesis is devoted to the consideration of this important question, so that
a brief reference need only be made here to some special points.

Cases of tuberculosis that simulate this disease are :—

1. *Chronic pulmonary tuberculosis with recurrent pyrexia.* The finding

of physical signs of pulmonary tuberculosis in the chest and of tubercle bacilli in the sputum tend to exclude the error.   Early cases with no tubercle bacilli in the sputum, no abnormal physical signs in the chest, and that run a relapsing temperature, are exceedingly difficult to differentiate, as they simulate the type with no enlargement of the external glands.

If enlargement of the spleen occurs, it is more likely that the case is one of lymphadenoma ; splenic enlargement is rare in chronic pulmonary tuberculosis, but, as Case XI shows, may occur.

The converse error is more likely to be made and the case of lymphadenoma to be taken for chronic pulmonary tuberculosis.   A definite decision can only be arrived at as the result of close observation of the patient and frequent examination of the sputum.

2. *Tuberculous adenitis with recurrent pyrexia.*   These cases mimic lymphadenoma with enlargement of the external glands.   If pulmonary tuberculosis is present the glandular enlargement is more likely to be a tuberculous adenitis.   Cases of the Sternberg type, in which the lymphatic glands alone are affected with tuberculosis, can only be differentiated, in the present state of our knowledge, by excising a gland under local anaesthesia and examining it under the microscope.

It is unfortunate that in the article on Lymphadenoma in Clifford Allbutt and Rolleston's *System of Medicine,* the statement is made ' that if the enlargement of the lymphatic glands be general it is almost certainly not tuberculous '.

The opsonic index to the tubercle bacillus in lymphadenoma.   In the course of the discussion on vaccine therapy, held by the Royal Society of Medicine in May and June, 1910 (*Proc. Roy. Soc. Med.,* iii, Supplement 49), L. Colebrook, in a statement based on the records of work in St. Mary's Hospital, said that ' in differentiation between these two infections (tuberculosis and lymphadenoma) the index has not served us, since in both it is abnormal to the tubercle bacillus '.

The examples that he alludes to are probably cases of chronic lymphadenoma. At any rate, in lymphadenoma with recurrent pyrexia, Colebrook's observation has not been confirmed.   The opsonic index to the tubercle bacillus was estimated in Cases II, III, and IV, and in every instance found to be normal.   I would specially refer to Case II, where the opsonic index was estimated during a bout of pyrexia and on each occasion found to be within the normal limits of 0·8 to 1·2.   The opsonic index to the tubercle bacillus in the case of tuberculous adenitis with recurrent pyrexia that so closely mimicked the external glandular type of lymphadenoma was, it will be observed, 1·37 after massage of the enlarged glands.

These facts are too few to argue from ; still, without entering into the question of the diagnostic value of the opsonic index, they suggest that, on further investigation, the index may prove to be of use in deciding whether one of these difficult cases is tuberculous or lymphadenomatous.

Treatment.   The patient must be kept in bed during the febrile period. Patients have been allowed to get up for a few hours each day without any effect

on the normal character of the temperature. In the afebrile period, up to the later stages of the disease, the appetite is excellent and the patient eats and digests food well. During pyrexia the appetite fails, and milk and slop-diet have to be administered. At the height of the fever it may be extremely difficult to get the patient to partake of food at all.

Cold sponging may reduce the temperature by a degree, but it quickly shoots up again to its original height. Antipyretics, such as antipyrin, quinine, and cryogenin, are proved to be of little value. It was interesting to note in Case III that injections of tuberculin in no way affected the temperature.

X-rays may cause external glands to diminish in size in chronic lymphadenoma, but appear to have no influence on this variety of the disease (Case V). As Case I showed, the rays may cause great pain and irritation in the affected glands, where for this reason they had to be discontinued.

The results in Batty Shaw's case show, similarly, that operative treatment is no safeguard against the onset of the acute form of the disease ; it may be required as a palliative measure to relieve pressure by the enlarged glands on the trachea.

Arsenic is the only drug for which any success is claimed (Dreschfeld). This, it may be remarked incidentally, suggests the possibility of a protozoal origin for the disease. A trial should, at all events, be made of the atoxyl preparations.

Clinical and Pathological Evidence.

In the course of investigating the relapsing fever of Hodgkin's disease it has been my good fortune to have under observation five cases displaying this form of pyrexia, no inconsiderable number when allowance is made for the rarity of this type of the disease. Four cases were males and one a female. The diagnosis of lymphadenoma was confirmed by microscopic examination in four of the cases during life, and in one case post mortem.

Two of the cases are dead and three are still living.

The first three cases had the superficial glands enlarged, and the size of the glands varied with the pyrexia ; the subjects, however, presented independent features, which enables one to relegate them to two distinct clinical types. The fourth case had no enlargement of the external glands ; the same is true of the fifth case at the present time, but there is definite evidence that enlargement of the glands occurred at a previous period.

Hence in all the cases a common type of temperature chart and of pathological lesion existed. The differences that they display in symptomatology, duration, and course are shown in the subjoined record of the cases.

Case I. G. P., aged 23, dispenser, was admitted to University College Hospital, under the care of Dr. Rose Bradford, on June 19, 1908.

His chief symptoms were loss of strength and lassitude. For the last nine months he had been weaker and subject to feverish attacks at intervals of a week to ten days. In November, 1907, he consulted a doctor who told him that he
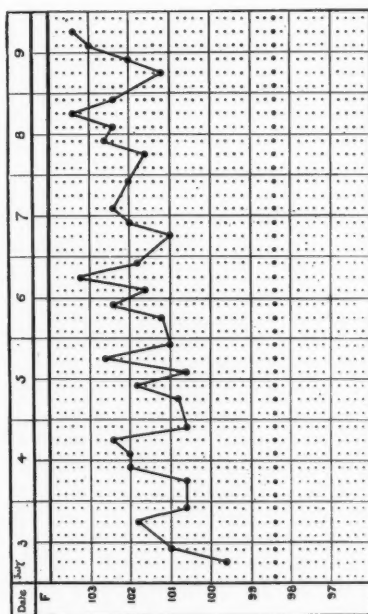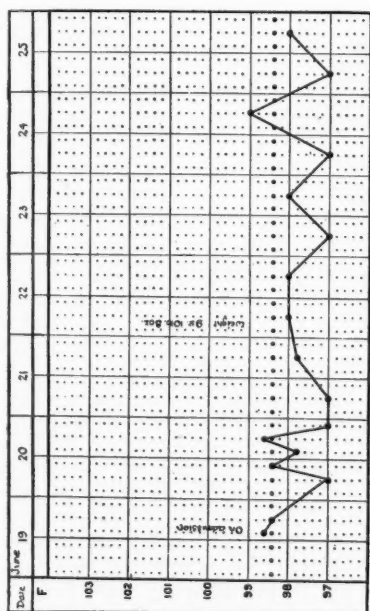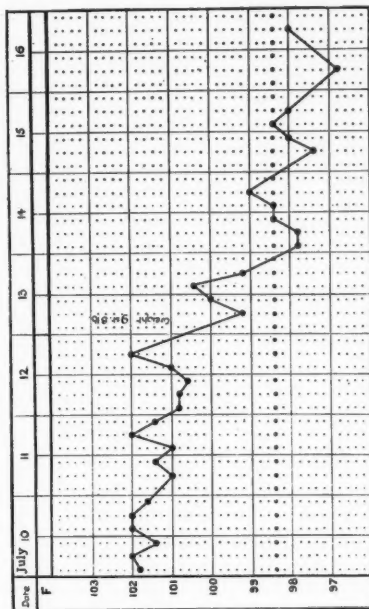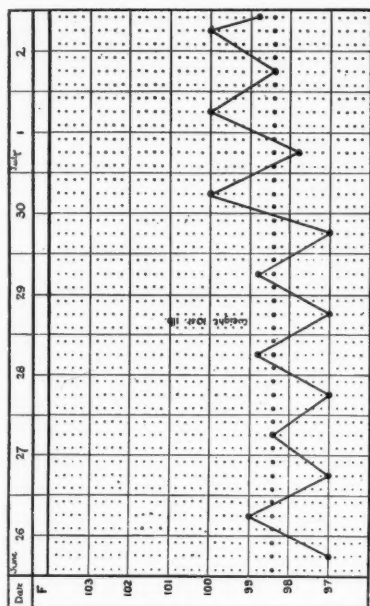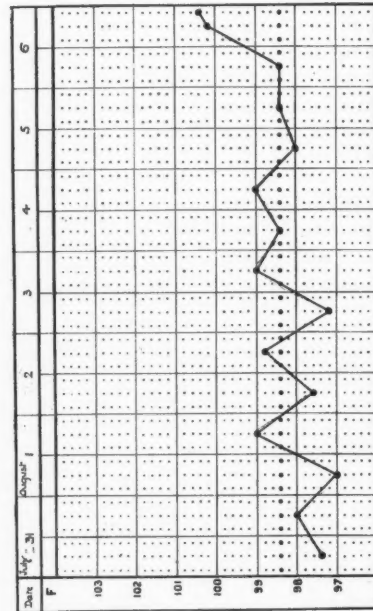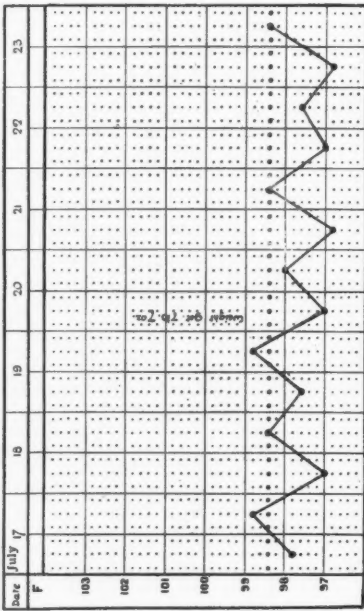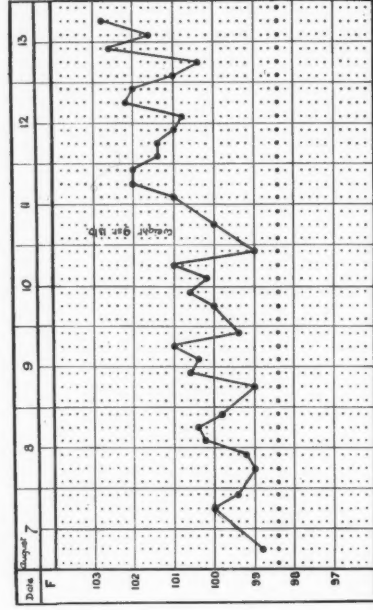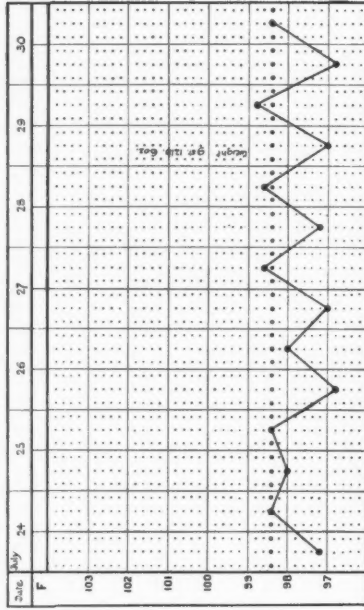
Case I.

Case I.

was suffering from anaemia. In April, 1908, the patient observed that the glands in his neck were enlarged and that they greatly increased in size and were sensitive during the feverish attacks.

There was nothing of importance in the history of past illnesses or in the family history of the patient. He had been able to continue his work up to the time of his admission to the hospital.

The patient was anaemic, and his skin had a grey-yellow tint; the sclerotics were not yellow. The temperature on admission was normal. Chains of glands could be felt on both sides of the neck round the sterno-mastoid and above the clavicle; they ranged from the size of a pea to that of a hazel-nut; they were discrete and freely movable; no signs of inflammation in or around them were present. One of the glands was removed under local anaesthesia and found to be lymphadenomatous on microscopic examination. No external glands were palpated in the axillae or groins. The spleen was not enlarged, and all the other body-systems were normal, except that the second sound was reduplicated at the apex of the heart.

The patient continued in this condition, with an occasional evening rise of temperature to 99°, until June 30, when the temperature reached 100° and he

Case I.

complained of headache and feverishness. On July 3 an ascending phase of pyrexia was definitely evident in the temperature chart, and the glands in the lower part of the cervical region on the left side were enlarging and becoming soft; acute pain over these enlarging glands was experienced. The spleen was just palpable below the costal margin. By July 7 the case presented its most remarkable but characteristic phase. The patient felt prostrate and extremely ill. The affected glands in both cervical triangles had gradually greatly enlarged; they varied in size from that of a pigeon's egg to a cricket-ball; they were painful to the touch, soft, and apparently adherent to the skin, which over them was inflamed and deep red in colour. The spleen was further enlarged, and some tenderness was experienced on palpation of the organ. The temperature at this date was 102.5° F. This condition lasted for about two days. On July 9, though the period of pyrexia was maintained, the temperature then being 102° F., both the glands and the spleen began to diminish in size and the patient felt better. The redness of the skin departed and the glands were no longer apparently adherent to it. The first pyrexial period terminated on July 14; at its close the patient perspired freely. The glands had now shrunk down to their original size and had ceased to be painful. In the intermission period the patient retained

his general symptoms of lassitude, but otherwise felt normal, both eating and sleeping well. On July 17 he was ordered exposure by the X-rays over the affected glands for twenty minutes, three times a week. The treatment, however, caused him a good deal of pain and aggravated his general symptoms, so after four sittings it was discontinued. August 7 : The glands again began to enlarge on the left side of the neck. Temperature 99·8°F., pulse 92. The patient felt feverish and 'out of sorts'. The second pyrexial period had commenced, and by August 11 the glands once more presented the remarkable features of great enlargement, softening, and tenderness that were noted in the first attack of fever. The temperature was 102°, the pulse 102, and the spleen was palpable one finger's breadth below the costal margin. Two days later its enlargement had increased to three fingers' breadth ; the patient had some slight vomiting ; subcutaneous oedema was present in the area of reddened skin. August 19 : The glands were still swollen, but their consistence was harder ; the spleen had diminished in size and the temperature was lower. The patient presented similar symptoms of prostration, sweating, and loss of appetite in the second pyrexial period.

On August 22 he was discharged from the hospital. The glands were again small, hard, and shotty, but the spleen could still be just felt.

Analysis of the temperature. The first period of pyrexia lasted fifteen days, the interval lasted twenty-two days, and the second period of pyrexia thirteen days. The highest temperature recorded was 103·4° F., which occurred on two occasions in the first pyrexial period. The time taken to attain the maximum temperature was eight and nine days respectively in the two periods.

Lysis terminated both periods ; it occupied four days. In each case the temperature fell to a subnormal level at the end of lysis.

The stage of high pyrexia was prolonged in both periods ; in the first period it occupied ten days, during which time the temperature never fell below 100° ; in the second pyrexial period it occupied six days. The highest temperatures were recorded in the afternoon or evening.

The charts show a first intermission period of eleven days, necessarily incomplete, for it was during the period that the patient was admitted to hospital, a second interval of twenty-two days, and a third (incomplete) of three days. In the intermission period the temperature was not continuously normal or subnormal, for exacerbations occasionally occurred to 99° in the afternoon or evening.

The pulse-rate increased with the rise in height of the temperature.

The patient lost a considerable amount of weight in the pyrexial period, which he regained to a certain extent in the interval of moderate pyrexia.

On leaving the hospital, the patient went to his own home at Ramsgate, where, for a space of three weeks, he appeared to recuperate rapidly ; he then had a pyrexial attack which lasted from twelve to fifteen days, the temperature rising several times to 103° F. He had another interval during which the symptoms ameliorated and his appetite for food returned. He undertook a visit to London, and while staying there a pyrexial period took place which kept him in bed for a month. Upon recovering from this he returned to Ramsgate, and for the following three months appeared to be fairly well. At the end of this time the last pyrexial period began, in which the patient died, six months after his discharge from hospital.

Terminal features of his illness were paroxysms of delirium (he was, however, fully conscious at the end), a burning pain in the abdomen, and great thirst.

Case II. E. G., a male of 17 years, by occupation a farm labourer, was admitted to the Brompton Hospital, under the care of Dr. Hector Mackenzie, on March 26, 1910, complaining of headache. The headache came on for the first time six weeks previously, lasted three weeks, and then returned after a fortnight's interval. There was no history of any
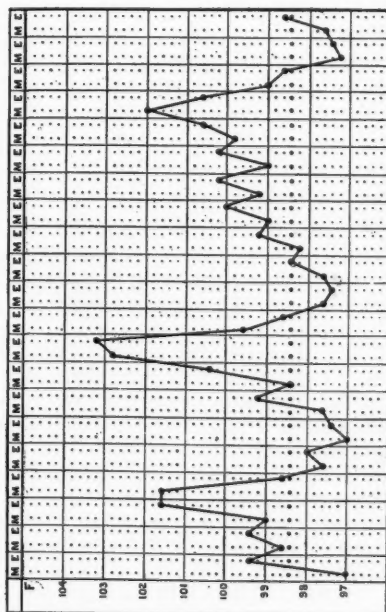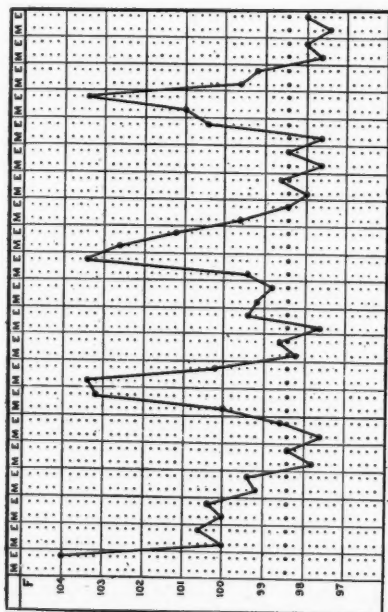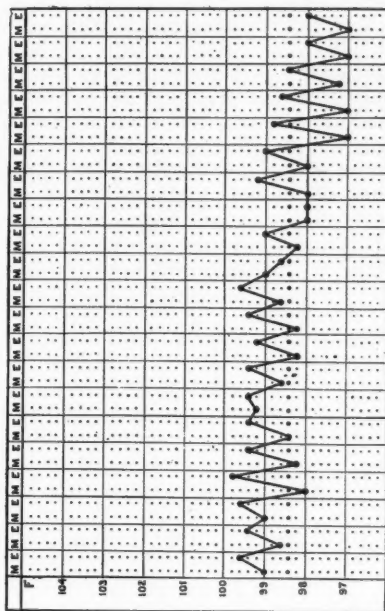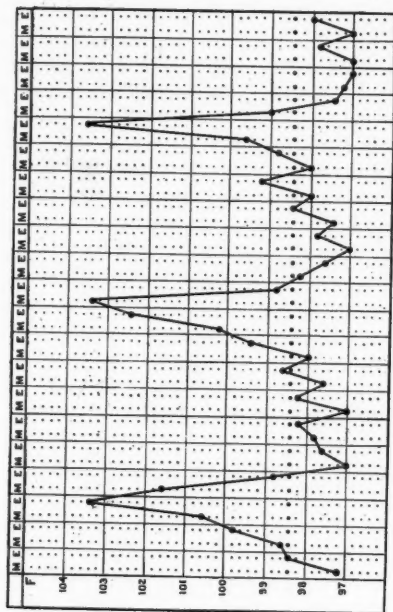
Case II.

previous illness or rheumatism.   His father died of ' cancer of the bladder'; his mother, two brothers, and two sisters are alive and well.

On admission the patient was fairly well nourished; he was very pale and looked ill, signs of old rickets were present in the bones, no external glands were palpable. T. 104° F., pulse 96, regular, of full volume and fair tension. The heart's apex-beat was situated in the fourth space just external to the nipple line; the impulse was somewhat diffuse and ' slapping' in character; no thrill. Limits of cardiac dullness were : upper limit, third rib; left limit, just internal to the nipple line ; right limit, half an inch to the right of the middle line.   At the apex the sounds were normal, but the first sound was followed by a faint systolic murmur ; a loud systolic murmur was heard over the pulmonary area ; a faint to-and-fro murmur was detected over the aortic area and the first sound over the tricuspid area was followed by a soft blowing systolic murmur.

Oedema of both ankles was present, specially marked on the left side. A few scattered râles were heard at both bases of the lungs posteriorly.   Nothing abnormal was detected in the abdominal, nervous, or urinary systems.

By March 31 the oedema of the feet and ankles had disappeared.   On April 2 for the first time a string of somewhat enlarged glands was felt in both posterior triangles of the neck.   The glands were hard, discrete, and fairly movable; they were not tender.   The spleen could not be felt.   The temperature was then 103° F., the appearance of the glands thus coinciding with a pyrexial period.   The cardiac murmur had disappeared.   Two days later one or two enlarged and hard glands were detected both in the axilla and the groin ; the glands in the former situation were tender.   The temperature was 99·5° F.

Synchronous with another marked pyrexial period, the temperature having reached 103° F., the affected glands on April 7 displayed a certain degree of enlargement and were tender.   A blood-count taken this day showed :—

| Total red corpuscles . | . | . | . | 4,200,000 per cubic mm. |
| „   white corpuscles | . | . | . | 52,200 „   „   „ |

Differential Count.

Polymorphonuclear neutrophils .	.	.	.	.	89·0 %
Eosinophils .	.	.	.	.	.	1·0 %
Lymphocytes, large	.	.	.	.	.	4·0 %
„ small	.	.	.	.	.	2·5 %
Hyaline leucocytes	.	.	.	.	.	3·0 %
Transitional	.	.	.	.	.	0·5 %

On April 12, by reference to the chart, it will be noted that the temperature rose again, the axillary glands enlarged somewhat, and the cardiac murmurs reappeared and were heard at the apex of the heart and over the pulmonary and aortic areas.   The heart's apex beat was in the fourth space, half an inch external to the nipple line.

On April 13 a murmur was only heard over the aortic area, and on the 15th the pulmonary murmur reappeared and was the only bruit detected.

The area of splenic dullness appeared rather increased.   The heart's apex beat was now in the fourth space in the anterior axillary line and the impulse was ' heaving' in character.

These cardiac signs, together with the appearance, disappearance, and reappearance of the murmurs, led to a consideration of the question of malignant endocarditis, and on the 25th 10 c.c. of blood were withdrawn from the left median basilic vein and cultured for organisms.   After eight days' incubation the culture proved sterile.

May 3.   During the night the patient was seized with a sudden and severe pain in the left side, and put his hand exactly over the splenic region to indicate

the locality of the pain. By the morning the severity of the attack had diminished. The area of splenic dullness had further increased, but no friction was heard on auscultation over the splenic area.

The physical signs in the lungs and heart were unaltered, except that the right limit of cardiac dullness now extended one inch to the right of the sternum.

A second blood-count gave the following result :—

Total red corpuscles . . . . 4,490,000 per cubic mm.
  ,,   white corpuscles . . . 19,000 ,, ,, ,,

Differential Count.

Polymorphonuclear, neutrophils . . . . 81·1 %
Eosinophils . . . . 5·0 %
Lymphocytes, large . . . . 6·5 %
     ,,   small . . . . 2·3 %
Hyaline leucocytes . . . . 3·7 %
Transitional . . . . 1·4 %

The *opsonic index* of the patient's blood to the tubercle bacillus was taken during the rise of temperature that occurred between May 7 and May 10.

The result of opsonic determination during the rise of temperature was as follows :—

Temperature.	*Opsonic Index.*
99·4° F.	0·80
99·2	0·90
99·0	0·85
99·8	1·05
101·2	1·10
101·6	1·11
102·8	0·90

It will be noted that all the opsonic figures fall within normal limits. (N.B.—For the last three temperatures the result is only approximate, as the patient's serum agglutinated the red cells used and digested the white cells. There was great difficulty in finding a sufficient number of normal white corpuscles to count.)

During the febrile period just referred to, all the glands of the body were enlarged and tender; on no occasion, however, did they reach such a degree of enlargement as that recorded in the first case, and there was no redness of the skin over the glands.

May 24. At this date the heart's apex beat was in the fifth space, half an inch internal to the nipple line. The right limit of cardiac dullness was at the right margin of the sternum. The heart's sounds were perfectly normal and no bruits were heard. The glands were still appreciably enlarged.

The following report was given by Dr. Greg after examining the chest with the Röntgen rays :—

'The lungs are transparent. The heart appears normal. On both sides of the sternum, above the heart, shadows project. These shadows are undulating in outline and suggest glands in the mediastinum.'

From May 26 the temperature, with the exception of some slight rises, remained normal, and the case ceased to exhibit relapses of pyrexia. The patient remained in pretty much the same general condition until June 10. On that date the glands generally were much diminished in size; none were now palpable in the right axilla. On June 17 the heart's apex beat was in the

fifth space in the nipple line, and the systolic murmur was again heard over the pulmonary area. The spleen could not be felt, nor was its area of dullness appreciably increased in size. The cervical glands remained as before, but only one small gland, about the size of a pea, could be felt in the left axilla. The physical signs in the lung had by this time disappeared.

On June 18 there is a note to the effect that the patient felt quite comfortable and got up for five or six hours daily. At the end of the day some slight oedema of the ankles was usually present. There were no cardiac bruits.

A gland was removed from the groin and found to be lymphadenomatous in nature.

The patient was discharged from hospital on July 1. Since that date he has been kept under observation as an out-patient.

His condition at the present time is as follows:—

He is still anaemic, but he has gained in weight and in health generally. He complains of no symptoms. The temperature is normal and has remained so since his discharge from hospital. He has small, shotty, discrete glands in the neck, the axilla, and the groin; the glands do not now enlarge and are not tender or painful.

Thus the case which had an acute onset has now merged into the chronic form of lymphadenoma.

Treatment. The drug given was arsenic; Ferri Arsenatis, gr. $\frac{1}{8}$ t. d. s., was given for part of the time, and afterwards two minims of Fowler's Solution in milk thrice daily. With a view to controlling the temperature ten grains of cryogenin were given on April 30, but the drug had no apparent influence on the pyrexial period, a temperature of 103.8° F. being registered on May 2.

The patient was kept on a moderate diet.

Analysis of the temperature. First period of pyrexia, 4 days; interval, 2 days. Second period of pyrexia, 2 days; interval, 2 days. Third period of pyrexia, 4 days; interval, 2 days. Fourth period of pyrexia, 3 days; interval, 3 days. Fifth period of pyrexia, 3 days; interval, 4 days. Sixth period of pyrexia, 3 days; interval, 3 days. Seventh period of pyrexia, 4 days; interval, 3 days. Eighth period of pyrexia, 4 days; interval, 2 days. Ninth period of pyrexia, 4 days; interval, 2 days. Tenth period of pyrexia, 7 days; interval, 2 days. Eleventh period of moderate pyrexia, 14 days; interval, 21 days.

The highest temperature recorded was 104° F. on admission to hospital. During the first six weeks of the illness, in the pyrexial period the temperature rose gradually in two to three days to a height of 103.5° F., and then fell by a lysis which occupied about 1½ days. This occurred, if the pyrexia on admission is taken as the height of the first period, on seven occasions, the characters of each pyrexial period thus showing a striking uniformity. The height of the next period was somewhat lower (101.8° F.), but the height of the ninth period was again above 103°.

In the tenth period, however, the ascent of the temperature curve was more gradual, taking six days to reach its height instead of two to three days, while the height attained was only 102° F. In the last period the pyrexia was very moderate and the height attained was but 100° F. From this time to the conclusion of the observations the temperature was normal, with occasional evening exacerbations to 99° F.

The highest temperatures were usually recorded in the evening; exceptions, however, occurred, a temperature of 103.5° being registered at 6 a.m, while a similar height was reached on two occasions at 2 p.m.

As the temperature rose the *pulse-rate* progressively increased and diminished again with lysis.

Case III. D. R., female, aged 8 years, was admitted to St. Thomas's Hospital under the care of Dr. Turney, on October 7, 1910. The symptoms for which she sought admission were attacks of feverishness, pain down the left side of ten days' duration, and a cough which came on a week previously.

History of present illness. The patient had glandular swellings in the neck two years previously. A year ago the glands on the left side of the neck were removed by Mr. Wallace in St. Thomas's Hospital. On microscopic examination the glands were found to be lymphadenomatous.

After the operation a few small glands could still be felt on the right side of the neck. She went to Margate to recuperate, and while staying there had occasional rises of temperature lasting four or five days; these attacks were associated with loss of appetite and dated from May, 1910.

Unaware of the histological examination of the glands, she was treated as an out-patient since August 10 up to the time of admission with injections of tuberculin every ten days. The dose started at 1/20,000 mg. and went up to 1/10,000 mg.

Past illnesses. Whooping-cough, measles, and chicken-pox.

Family history. Unimportant, except that her eldest sister, now aged seventeen, had a lump removed from her neck at the age of five.

State on admission. The patient was a pale child with a hectic flush over the malar bones; she was in no respiratory distress. Enlarged glands were palpable above both clavicles. Temperature 101° F., pulse 132, respiration 40.

Respiratory system. The right lung was normal; there was dullness at the base of the left lung up to the level of the third rib and the second thoracic spine. The breath-sounds on the right side of the chest were exaggerated, but were normal in character. Over the dull area on the left side the breath-sounds were only weakly transmitted, and they were heard better behind than in front.

Cardiovascular system. The area of cardiac dullness was fused with the dull lung area on the left. Nothing abnormal was detected in the abdomen or in the other systems of the body.

October 12. The pyrexial period had now ceased, and it was found that the breath-sounds were now quite well heard over the left base, while the percussion note was now only slightly impaired. This variation in the physical signs was observed to a certain extent in the apyrexial period; thus, on October 15 the pulmonary signs were similar to those on admission, while on the 19th the left chest was again resonant.

On October 24, with the manifestation of the second pyrexial period, the physical signs had undergone a rapid transformation; the whole of the left chest was dull to percussion, and the breath-sounds were distant and bronchial in character. Associated with these features was a troublesome cough, relieved by sitting up in bed.

November 3. The temperature was now afebrile; the left apex was now resonant, but the dullness and weak breath-sounds at the left base persisted. Mediastinal dullness could now be elicited one inch to the right of the mid-line of the sternum and one and a half inches to the left.

The spleen was palpable for the first time, one and a half inches below the costal margin, and the liver dullness extended one inch below the costal margin.

November 9. During the beginning of the third pyrexial period the left chest was once more resonant and the breath-sounds distinctly heard. It was noted that the supra-clavicular glands had enlarged with the onset of pyrexia.

November 15. Lysis had now commenced; but the glandular enlargement had further increased, while the left side became completely dull to percussion and the breath-sounds were weak and bronchial. The apex beat of the heart could be felt in the sixth space in the nipple line; the second sound was accentuated at the apex and was very loud over the tricuspid area.

The spleen was larger and the notch was easily felt at its lower end
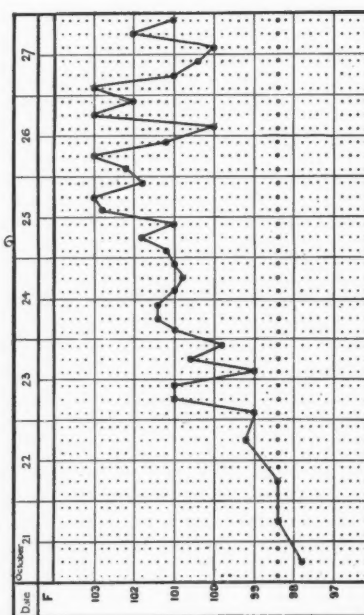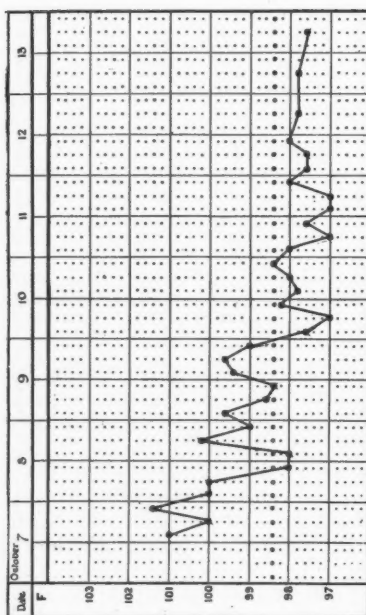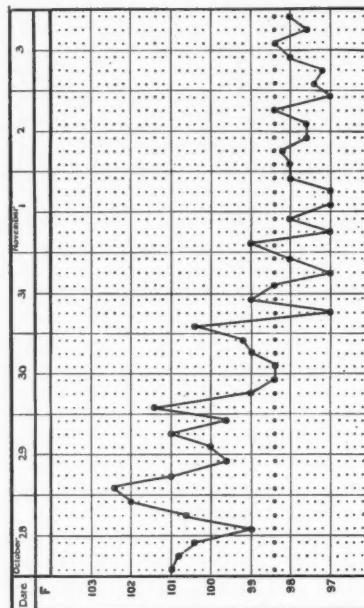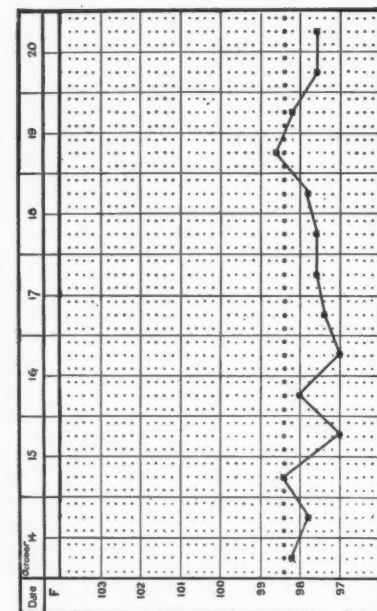
Case III.
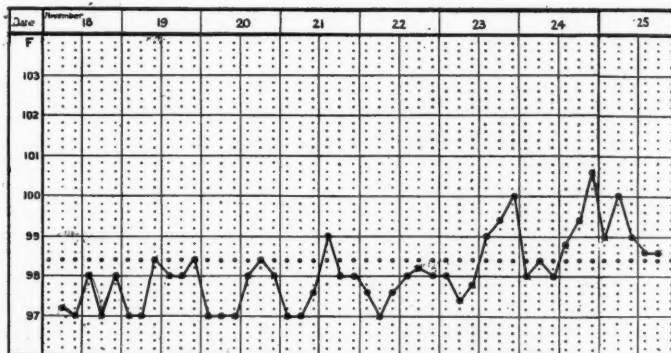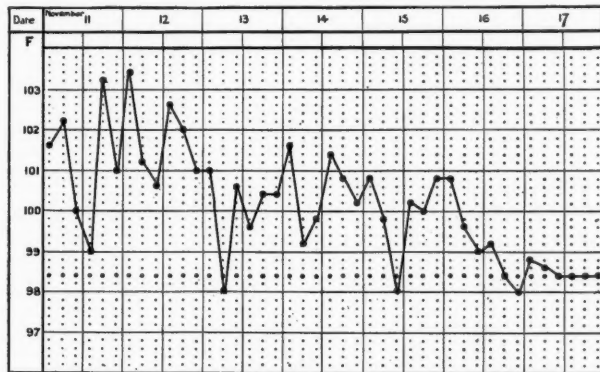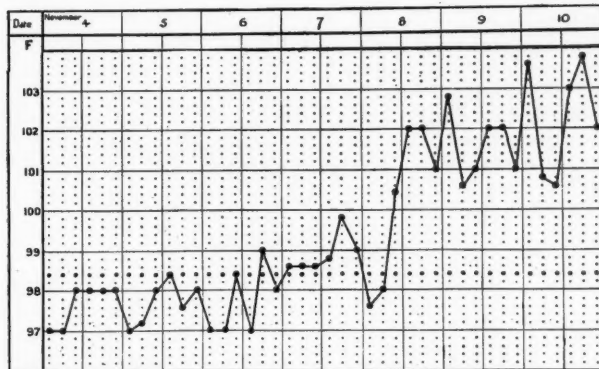
Case III.

internally. The organ reached to two and a half inches below the costal margin
the liver did not increase in size.

November 22. For the last six days the temperature had been normal;
the masses of glands in the neck were much smaller, especially on the left side;
the glands were discrete and movable. The pulmonary dullness on the left side
had again disappeared.

The patient felt much better. On the 23rd, however, another pyrexial
period set in, the general symptoms of malaise and irritability returned. During
this attack she left the hospital by the wish of her parents on November 25.

The following investigations on the case are recorded:—

Examination of the Blood.

Red corpuscles	3,962,500 per cubic mm.
Haemoglobin	60 %
Colour index	0·7 %
White corpuscles	10,500 per cubic mm.

Differential Count.

Polymorphonuclear leucocytes . . .	77 %
Eosinophils	2·6 %
Small lymphocytes	13·2 %
Large lymphocytes	3·2 %
Large hyaline cells	3·2 %
Plasma cells	0·4 %
Basophils	0·4 %

X-ray examination. October 18, 1910. There is a wide shadow along the
right side of the sternum. This has a sharp margin. Shadows with an irregular
margin are present on each side of the heart, and much the larger on the left;
there is nothing to indicate whether these are derived from the mediastinum or
the lungs. The shadow on the right edge of the sternum is certainly due to a
widening of the mediastinum; it has no projection on its edge.

The right side of the diaphragm moves freely; the left side is almost
motionless.

Von Pirquet's reaction to both bovine and human tuberculin was negative.

Analysis of the temperature. First period of pyrexia, 3 days (incomplete);
interval, 12 days. Second period of pyrexia, 10 days; interval, 5 days. Third
period of pyrexia, 11 days; interval, 6 days. Fourth period of pyrexia, 3 days
(incomplete).

The patient was admitted towards the close of a pyrexial period. The
highest temperature recorded was 103·8° F. during the third pyrexial period.
The chart is a very typical one, for in each complete period of pyrexia there is
a gradual ascent to a maximum temperature which occupies from three to four
days; then comes a fastigium of about five days, during which time the
temperature at some period of the day always exceeds 102°, and finally the period
terminates by a lysis of three to four days. In each case the temperature fell to
a subnormal level at the end of lysis; during the apyrexial interval the tempera-
ture was invariably normal or subnormal. The highest temperatures were
usually recorded in the evening, but it will be again noted from inspection of
the chart that several exceptions occurred to this rule. As in Case II, the pulse-
rate increased with the rise of temperature and diminished with the fall. Both
the pyrexial and the apyrexial periods were sustained in duration over several
days; the two complete pyrexial periods were of longer duration than their
corresponding intervals.

Case IV. H. J., a male of 34 years, a commercial traveller, was admitted to Brompton Hospital, under the care of Dr. S. H. Habershon, on October 27, 1909. He gave the following history:—

In March, 1909, he had an attack of what was taken to be 'influenza'. From that date he was subject to 'chills' at intervals, and was unable to follow his occupation owing to progressive weakness and lassitude. He had a slight cough and some expectoration. He thought that he had lost weight. Of late he had been having profuse night-sweats. He had never had an haemoptysis. There was no history of any previous illness.

Family history. Father died of gastric ulcer. Mother died of pulmonary tuberculosis at 42 years of age twenty-four years ago. Six brothers and three sisters are alive and well. He was a married man; the wife was healthy, and he had one child, a girl of six years, who was healthy.

On October 22 he was seen by a physician during one of these chills. The temperature was 102° F. at midday and 103·2° F. two days later.

On admission the patient was noted to be very anaemic. The chest was rather flat, thin, narrow, and poorly covered.

The percussion note was slightly impaired at the right apex, but apart from this nothing abnormal was detected on physical examination. The spleen could not be felt and no enlarged glands were detected. Temperature 97° F., pulse 80, respirations 20.

The patient, after being kept in bed for five days, was allowed up for two hours, and then by stages of four hours to six hours without, apparently, any effect on the temperature.

It was not until November 6 that the patient began to present remarkable and at first puzzling features. On the evening of this date the temperature quickly rose to 102° F. and the patient perspired profusely. He did not complain of any definite symptoms, but experienced a feeling of general malaise; there was no alteration in the physical signs to account for the pyrexia.

After a pyrexial period of eight days the temperature on November 14 fell by lysis to normal; the patient expressed himself as feeling much better.

A provisional diagnosis of early pulmonary tuberculosis was made, and in the absence of marked physical signs in the chest and the then present normal temperature the question was considered of transferring the patient to the Brompton Hospital Sanatorium, provided that confirmatory evidence of tuberculosis was obtained. This favourable opinion was, however, rudely shattered by the advent of the second pyrexial period on November 23. On December 1 the temperature was descending by irregular lysis, and on this date for the first time the spleen was discovered to be enlarged and palpable one inch below the ribs; slight tenderness of the spleen was elicited. Every effort was made to discover the focus that gave rise to this remarkable pyrexia.

Physical examination only confirmed the daily initial note on the case. The radiographer reported that nothing abnormal was detected in the chest, and that the apices of the lungs were quite transparent. A culture made from a catheter specimen of urine grew only a staphylococcus; no tubercle bacilli were present in the urine.

On November 28, 10 c.c. of blood were taken from the right median basilic vein. A culture made from the blood proved sterile. With regard to the patient's opsonic index blood examination showed:—

(1) Index to tubercle bacilli, 1·03 November 25, and 0·63 November 29.
(2) Index to staphylococci, 0·97 November 29.

Blood films were made daily during the second pyrexial period and stained both by Leishman's and Giemsa's methods. No parasites, malarial or otherwise, were discovered.

Widal's reaction for the typhoid bacillus proved negative. The faeces were examined microscopically and nothing abnormal was found.
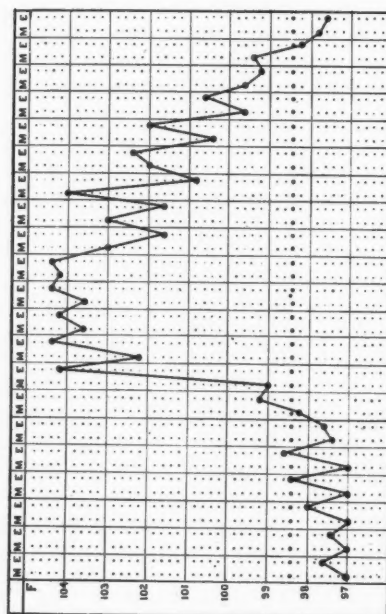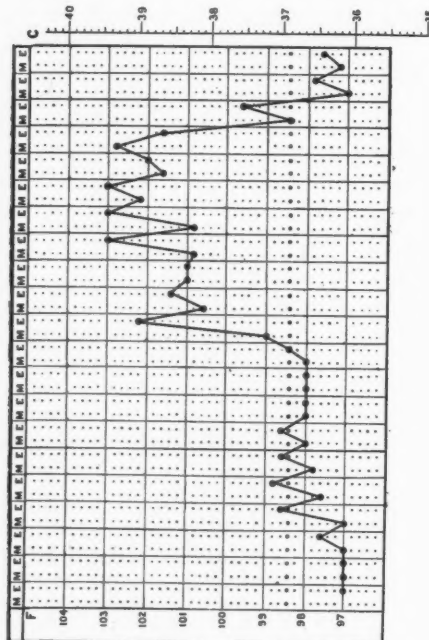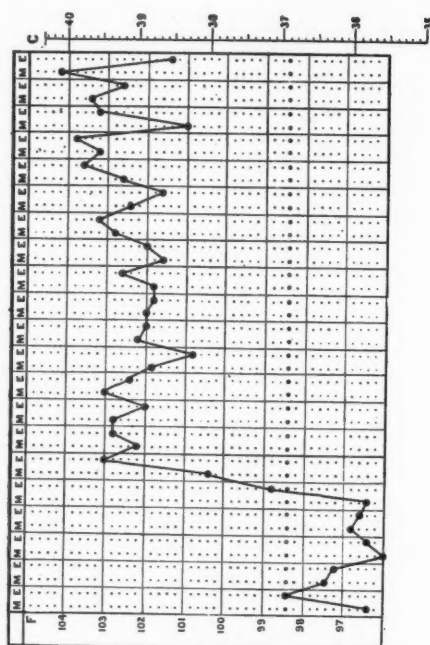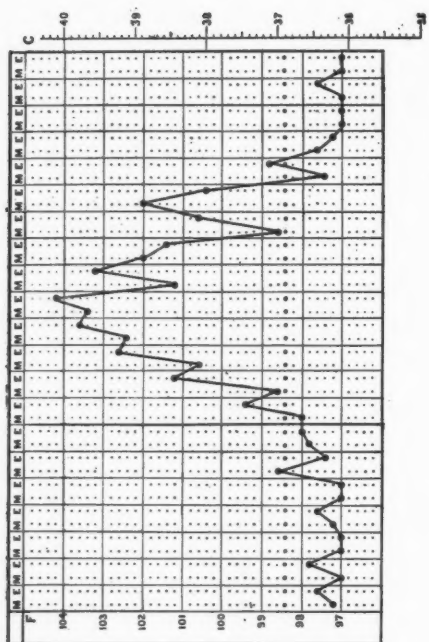
Case IV.

The patient vomited on November 27, in the early morning, and again on the 28th.

December 10. It was noted that the spleen reached to the seventh rib in the mid-axillary line, and could just be felt below the costal margin.

A blood-count taken this day gave the following result :--

| Total red corpuscles . | . | . | . | 4,700,000 per cubic mm. |
| „   white corpuscles | . | . | . | 9,064 „   „   „ |

Differential Count.

Polymorphonuclear leucocytes	.	.	.	.	59·5 %
Lymphocytes, large	.	.	.	.	.	12·5 %
„ small	.	.	.	.	.	22·0 %
Eosinophils	.	.	.	.	.	.	6·5 %

On December 16 a second blood examination gave a similar result, a normal proportion of the various cell-elements being present and no abnormal elements being found.

During the third pyrexial period, on December 17, while the temperature was 104·2° F., the patient was very collapsed and the surface of the body cold and clammy. Insomnia now began to be a troublesome feature of the case.

December 20. During the night the patient was delirious and attempted to get out of the window of his ward. In the morning his mental condition was still confused; he could not remember how long he had been in hospital, and he was violent in his actions. Temperature 103° F.

December 21. Temperature 104° F. Patient had no sleep during the night and talked incoherently on subjects of a religious nature. He lay on his back with his knees drawn up, and explained that it gave him pain to straighten the limbs. Hypodermic injections of morphia (ɑ v) quieted him to some extent.

A new feature of the case was retention of urine, and a catheter had to be passed night and morning. There was apparently a spasmodic stricture of the urethra, as a gum-elastic catheter was gripped eight inches from the meatus.

December 26. By this date the pyrexial period had terminated and the patient's mental condition had so far improved that he was able to answer questions rationally. He was much weaker, and wasting of the body had become a most marked feature. Repeated examination of the fundus oculi failed to reveal anything abnormal.

On December 30 there is a note to the effect that the enlargement of the spleen cannot now be felt.

On January 1, 1910, the patient was much worse. He was flushed, hot, and very restless; at intervals he threw his head about as if in pain; no food or medicine could be taken. Temperature 99·8° F.

His condition at this juncture was looked upon as hopeless, but on January 3 an extraordinary change occurred without any apparent effect on the course of the temperature, which was then pyrexial. When seen in the morning the patient was quite rational and recognized every one around him. He passed eight ounces of urine voluntarily and slept soundly afterwards. He had been able to assimilate very little nutriment, but began to take his food much better; wasting and weakness were now extreme. The improvement was only a transitory feature of the case.

On January 21 he experienced some difficulty in articulation, and wandered at intervals; he was also very drowsy.

January 28. Mental condition had again improved. The spleen could just be felt.

February 4. The heart was beating very tumultuously. Pulse-rate 160 +. Patient slept for most of the day, but when awake was quite clear in his mind.

He was pallid in countenance and it was clear to all around him the end was gradually approaching.

On February 10 the patient was so collapsed that on two occasions no temperature could be obtained, the mercury in the thermometer not rising even to 95°. The pulse was almost imperceptible at the wrist and exceedingly frequent. Incontinence of faeces and urine was present.

A blood-count gave the following result :—

Blood very watery and pale. Red corpuscles show vacuolation ; no poikilo-cytosis or anisocytosis.

Total reds	2,788,000 per cubic mm.
„ whites	7,300 „ „ „

Differential Count.

Polymorphonuclear leucocytes	65 %
Lymphocytes, large	13 %
„ small	16 %
Hyaline leucocytes	3 %
Transitional	3 %

From February 12 to 17 the patient again rallied to a slight degree. On the 17th the temperature once more began to rise. On the morning of the 18th the patient was quite comatose ; the pupils were dilated and did not respond to light ; the breathing was slow and stertorous. He died at 10.10 a.m.

Post-mortem examination nine hours after death. The body was extremely emaciated ; there were purpuric patches about the feet and on both sides of the neck with slight oedema of the ankles. The brain was normal ; the pericardium contained a little excess of free fluid ; the heart was normal, the arteries were free from atheroma, and there was no thrombosis of the iliac veins. *Liver,* soft ; *the kidneys* were normal. The pleurae were free except at the apices of the lungs, where there was evidence of old adhesions. The lungs were congested and oedematous at the bases. There was no evidence of tuberculosis.

The most striking post-mortem changes were seen in the spleen and in the internal glands of the body. *The spleen* was much enlarged ; it weighed 22 ounces. In the substance of the organ were numerous small yellow patches ; other patches were deep red in colour ; all the patches were harder than the surrounding substance. A culture taken from the spleen proved sterile.

The submaxillary, cervical, axillary, and inguinal glands were dissected out, but on section were normal, showing no deposit of lymphadenomatous tissue. The inter-bronchial glands were enlarged and showed a few grey-white centres. Both the superior and posterior mediastinal glands were enlarged and showed yellow-white areas. The same abnormalities were true of the mesenteric and lumbar glands. One gland near the lesser curvature of the stomach was enlarged, showed caseous patches, and in one part a haemorrhagic area. There was uniform enlargement of the thyroid gland, but on section it appeared quite normal.

Analysis of the temperature. First period of pyrexia, 9 days ; interval, 8 days. Second period of pyrexia, 9 days ; interval, 11 days. Third period of pyrexia, 14 days ; interval, 5 days. Fourth period of pyrexia, 22 days ; (moderate pyrexia) interval, 5 days. Fifth period of pyrexia, 13 days ; interval, 4 days. Sixth period of pyrexia, 4 days to death.

The highest temperature recorded was 104·8° F. on five occasions. The two first periods of pyrexia lasted for the same number of days ; as the illness progressed the periods of pyrexia increased in duration. Between the fourth and fifth periods the temperature did not remain normal or subnormal, but a period of

moderate pyrexia existed; this, it will be remembered, was also a feature in the latter stages of Taylor's third case. The days taken to attain the maximum temperature differed in the several periods; thus the ascent occupied four days in the first, five days in the second, three days in the third, two days in the fourth, and six days in the fifth periods.

Unlike Case II, in which after the maximum had been reached the temperature began to fall by lysis, in the present instance a high degree of pyrexia was
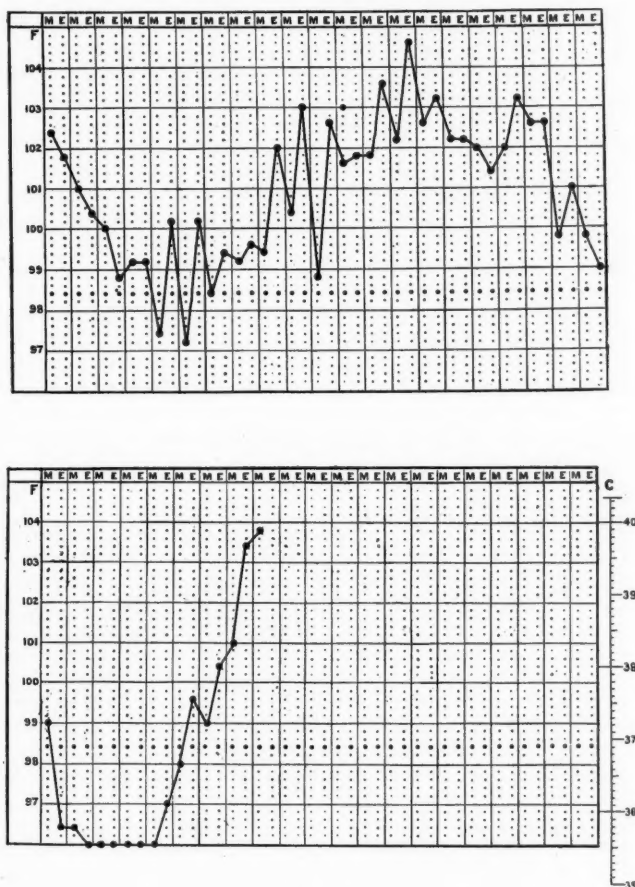
Case IV.

maintained for several days; this is especially marked in periods I and III; in period I the maximum temperature, 103° F., is recorded on four occasions; in period III the maximum temperature fluctuates between 104° and 105° for six consecutive days.

Lysis occupied two days in the first, four days in the second, the long time of seven days in the third, five days in the fourth, and three days in the fifth periods. In each of the five pyrexial periods a reference to the chart will show that a temporary rise of temperature occurred after lysis had begun, and following on this lysis was resumed. In the first period, for example, a rise to 99·8° was registered after the temperature had already fallen to normal; the same thing

occurred in period II, the temperature rising again from normal to 100·8° and then to 102° F., after which lysis was resumed. With what may be termed secondary lysis the temperature in each case fell to below normal, like the crisis of a pneumonia chart. The highest temperatures were recorded in the evening and in the majority of instances at 8 p.m.

The pulse-rate progressively rose with the temperature and diminished again with lysis, as in Case II. It will be noted that death occurred during a pyrexial period, the last temperature charted being 103·9° F.

Case V. G. N., a male of 21 years, was admitted to Brompton Hospital on August 17, 1910, complaining of general depression and occasional attacks of giddiness. Three years ago he was in the London Hospital for ' glands of the neck'. He had then no pyrexia. One of the glands was excised from the posterior cervical triangle, and through the courtesy of Dr. H. L. Tidy, the medical registrar, I am informed that the gland had the typical structure of lymphadenoma. A year ago the glands enlarged considerably ; the patient states that there was a bunch as big as a fist on the left shoulder !

He again attended the London Hospital, and the glands were exposed to the X-rays. The patient had about seventeen sittings varying in duration from ten minutes to one and a half hours. At the end of the treatment the glands had disappeared. The skin was inflamed, there being probably a certain amount of X-ray dermatitis. For the last eight months he had been liable to chilly sensations and sweatings, and since August 13 had felt feverish.

Since September, 1909, he had been liable to pains in the back and a feeling of great lassitude ; these sensations lasted for fourteen to twenty-one days with intervals of three days to three weeks, during which the patient felt quite well. One month previously he had an attack of ' pleurisy ' in the left side (this may possibly have been perisplenitis). He had never noticed any swelling of the ankles, and had never lived abroad or had malaria. There was nothing of note in the family history.

On admission the patient was pale but well nourished. Pulse 120. Temperature 103° to 102° F. A scar was present in the left posterior triangle. There was no enlargement of the superficial glands. The heart was normal in position. At the apex a soft systolic murmur was heard accompanying the first sound. Examination of the respiratory system revealed nothing abnormal except that there was some deficiency in the air entry at the base of the left lung.

The spleen reached from the seventh rib above to one inch below the costal margin. It descended for about two inches with respiration and the edge could be definitely felt. The liver was not enlarged, and the kidneys were non-palpable. The patient had an undescended right testicle, the left testicle was in the scrotum. The pupils reacted well to light and to accommodation. There was nothing abnormal on examination of the fundus oculi. Von Pirquet's reaction negative. During the first period of pyrexia (August 17 to 22), the patient looked and felt ill ; his appetite was poor and the tongue furred.

A blood-count made on the 21st gave the following result :—

Total red corpuscles	3,500,000 per cubic mm.
,, white corpuscles . . .	5,000 ,, ,, ,,
Haemoglobin	60 %
Colour index	5 %

Poikilocytosis and polychromatophilia.

Differential Count.

Polymorphonuclear leucocytes	55 %
Lymphocytes, large	3 %
,, small	5 %
Hyaline	12 %
Transitional	6 %
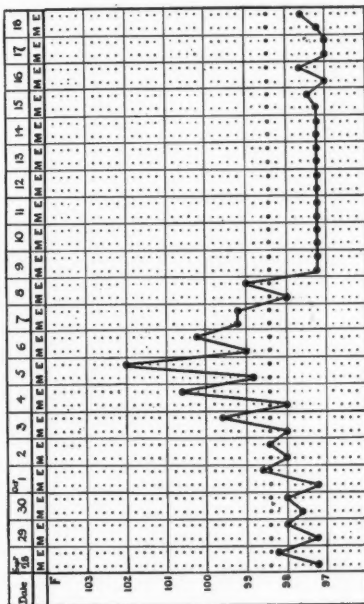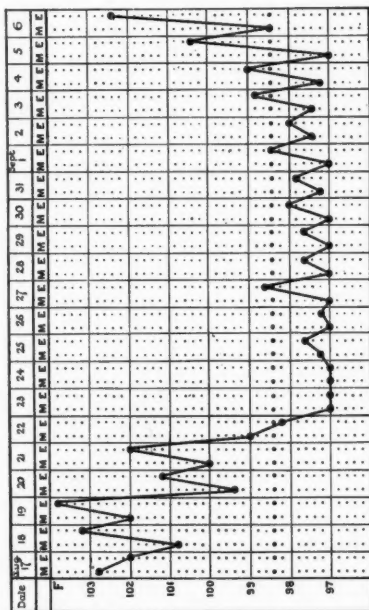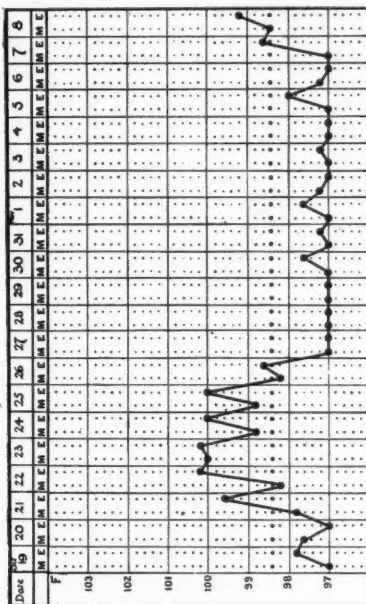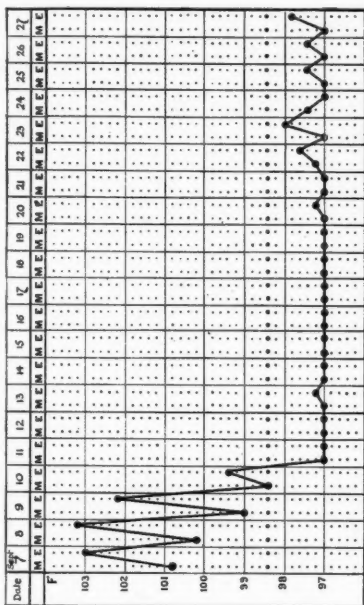
Case V.
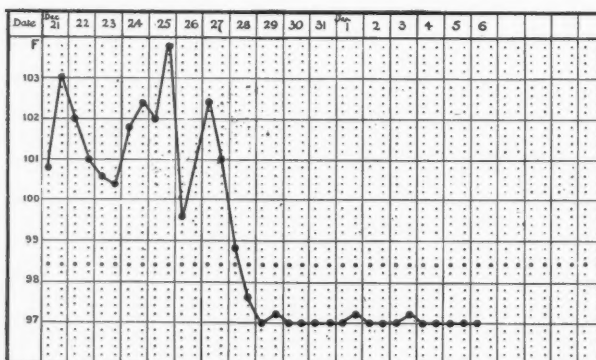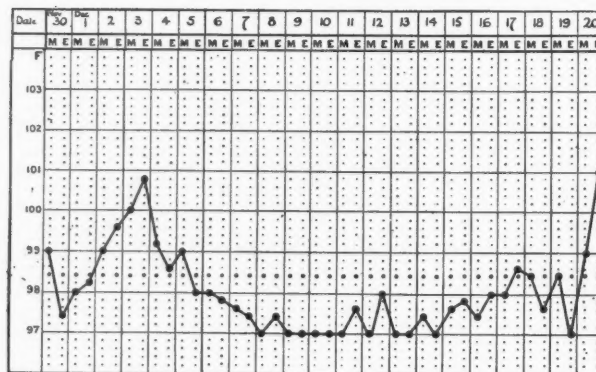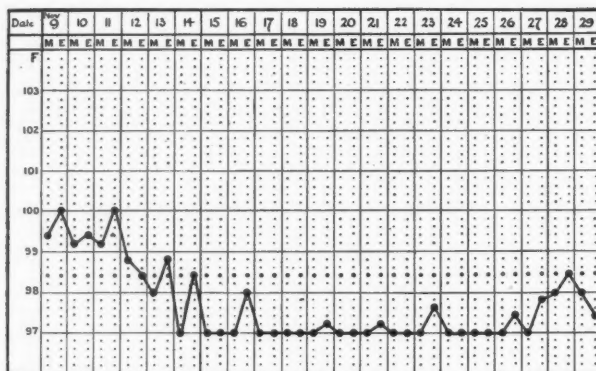
Case V.

At the end of the pyrexial period (August 22) the patient felt much better.

On August 27, at 7 a.m., he had some general twitchings, and passed the rest of the day in an irresponsible condition, tossing from side to side on his bed and groaning frequently. The pupils were dilated. The patient vomited twice during the day. Towards evening he became quieter and eventually slept.

On the date of this attack the temperature was normal. On the next morning he awoke in a perfectly rational condition.

On September 18 the spleen was just palpable in inspiration one inch below the ribs.

On the following day it was palpable two inches below the ribs, and the patient complained of pain in the region of the spleen.

A systolic murmur was heard over the pulmonary cartilage. At this juncture the second pyrexial period occurred. By the 15th the splenic pain had diminished and the organ was non-palpable. The temperature was subnormal.

October 9. On this date, which marked the termination of the third pyrexial period, the spleen was again palpable, and came down to one inch below the costal margin during inspiration. It was hard and had a well-marked edge.

During the following afebrile period the spleen diminished in size, but has remained up to the present time enlarged to a certain extent, both in pyrexial and apyrexial periods, that is to say, it increases in size with pyrexia. It was palpable two inches below the costal margin on October 11, and in the afebrile periods its edge could just be felt.

During the attacks of relapsing fever the patient has suffered from the general symptoms of lassitude, headache, and malaise.

Examination with the X-rays failed to reveal the presence of enlarged glands in the mediastinum or other abnormal conditions in the chest. The examinations were made both in pyrexial and apyrexial periods.

Splenic puncture has been performed on two occasions during pyrexial periods. The first exploration was made on October 6 (third pyrexial period), when the temperature registered 100° F.; the second was carried out on October 24 (temperature 100°), in the fourth period of fever. Smears were made from the splenic blood in the two experiments and broth cultures prepared. In every case the cultures proved sterile. The films were stained by the following methods:—Giemsa, Leishman, Gram, and Ziehl-Neilsen. On microscopic examination they revealed the usual features of a smear taken from the normal spleen. No abnormal cells were observed, and no protozoa, bacteria, or other parasites were detected.

Analysis of the temperature. The patient has been under observation for a period of 118 days, and the temperature chart records six intervals of well-marked pyrexia. The highest temperature recorded was 104° F. in the first pyrexial period. It was during this period that the patient was admitted to hospital.

First period of pyrexia, 6 days (incomplete); interval, 11 days. Second period of pyrexia, 8 days; interval, 22 days. Third period of pyrexia, 6 days; interval, 12 days. Fourth period of pyrexia, 5 days; interval, 12 days. Fifth period of pyrexia, 7 days; interval, 16 days. Sixth period of pyrexia, 6 days; interval, 6 days.

The highest temperatures were usually recorded in the evening. One of the most salient features of this chart is the pronounced subnormal temperature of the afebrile intervals. In the exceptionally long second afebrile period, which extended over twenty-two days, the temperature remained at a dead level of 97° for eleven days; it behaved exactly the same in the other apyrexial periods, though for shorter periods of time. So marked, however, was this subnormal tendency of the temperature that we are able in the afebrile periods to trace the advent of a pyrexial outburst by an ascent of the temperature from the sub-

normal to the normal. This is clearly shown in a consideration of the range of temperature that took place towards the end of the second afebrile period and during the commencement of the third pyrexial interval. The bouts of pyrexia display the features that have already been noted in the record of the preceding cases ; the gradual ascent, the fastigium, and the lysis are all demonstrated.

The pulse-rate again increased in the pyrexial and diminished in the apyrexial intervals. The highest temperatures occurred in the first and second periods of fever.

The Pathological Evidence.

Histological examination of the glands in the five cases recorded in this thesis demonstrated their lymphadenomatous nature. It has been found possible to correlate the appearances of the glands with the various stages of lymphadenoma as described by D. M. Reed and Longcope. The gland-sections in the several stages fully confirm the work of these observers.

Technique. The glands were fixed in formalin (10 per cent.), hardened, embedded in paraffin-wax, cut and the sections stained with haematoxylin and eosin or by van Gieson's method.

The pathological evidence in each case may now be briefly noted :—

Case I. Gland excised during life from the cervical region. The section shows an intermediate stage in which the cellular character of the pathological process is still marked, but at the same time the connective tissue has already commenced to proliferate and to replace the cells. Coarse, anastomosing bands of fibrous tissue are apparent, bounding small cell-containing spaces. In some parts of the gland nothing but dense fibrous tissue is to be seen ; in other regions the cell-groups are large ; there is hyperplasia of the lymphoid cells, and an increase of the reticulum, which contains lymphocytes, plasma cells, and poly-morphonuclear leucocytes ; epithelioid cells and a few 'giant cells' are present. (Plate 5.)

Case II. Gland excised during life from the groin. The section exhibits a hyperplasia of the cellular elements with proliferation of the reticulum. Trabeculae of young connective tissue are already evident in the section. The cells of lymphadenoma (lymphocytes, leucocytes, plasma cells, epithelioid cells) are present in infinite variety. Mitosis is well marked. The most striking features noted are the great abundance of eosinophils and the large mono-nuclear and multinuclear 'giant cells'. (Plates 6 and 7.)

Case III. Cervical gland excised during life. For the pathological evidence in this case I am indebted to Dr. H. G. Turney. The pathologist, St. Thomas's Hospital, reported that the section displayed the characteristic features of lymphadenoma.

Case IV. Internal lymphatic glands (mediastinal and lumbar) examined post mortem. The sections show a great increase in the connective tissue, the cellular element being almost entirely absent. The gland is converted into a meshwork of coarse fibrous tissue; a few small collections of cells survive in some of the spaces that are bounded by connective tissue. The cells are broken down and degenerated. The glands thus correspond to Longcope's advanced stage of lymphadenoma.

The spleen. Lymphomatous areas were present. The cells in these areas were similar to those seen in lymphadenomatous glands; in many instances the

cells were broken down and degenerated. The connective tissue was greatly increased and was responsible for the hard nature of the areas as compared with the rest of the spleen substance.

Case V. Cervical gland excised during life. I am indebted to Dr. H. L. Tidy, medical registrar to the London Hospital, for a report as to the lymphadenomatous nature of the gland excised in this case.

Recurrent Pyrexia in Tuberculous Adenitis and Chronic Pulmonary Tuberculosis.

The records of these five cases, each definitely proved to be lymphadenomatous in nature, support the statements of Gowers and Taylor that a definite variety of Hodgkin's disease exists in which the temperature is of the relapsing type.

I am also enabled to fully confirm the observations both of Dreschfeld and Taylor, which were based on the clinical features of their cases, and were to the effect that relapsing pyrexia may be present in lymphadenoma without enlargement of the superficial glands. Taylor, in the paper which has already been referred to at some length, laid great stress on the importance of the temperature chart in the special variety of lymphadenoma now under consideration, and maintained that the character of the pyrexia was diagnostic of the disease, though he was unfortunately debarred from giving pathological proof of his statement.

If we turn back once more to the record of Case IV it will be apparent from the line of clinical investigation pursued that considerable difficulty was experienced in arriving at an accurate diagnosis of the case. The patient came into Brompton Hospital as an early case of pulmonary tuberculosis, and almost up to the time of his death the probability of this assertion might have been maintained. It is true that the character of the temperature chart and acquaintance with the literature help towards the formation of an accurate diagnosis; the temperature chart was, however, a secondary argument, the primary one being that there was no evidence of tuberculosis present.

The observation as to the similarity of acute Hodgkin's disease and tuberculosis is by no means a new one; indeed, as Osler remarked in the course of a discussion on a paper read by Joseph Sailer before the College of Physicians, Philadelphia, in 1901, it was made many years before Sternberg was born !

Morgagni in 1652 described a well-marked case of tuberculous adenitis in a boy aged fifteen : ' The glands beneath the jaw, in the neck and thorax, were all enlarged, and tumours of the same character existed in the integuments of the abdomen and in the abdominal cavity. The progress of the disease was rapid and accompanied with fever.' After death all the glands of the body were found to be ' strumous '.

Gowers alluded in 1879 to the fact that a differential diagnosis between

such cases and lymphadenoma is almost impossible, and can only be made by the occurrence of secondary softening in the glands (Reynolds's *System of Medicine*).

It is well known that lymphadenoma with all its varieties has been considered simply an aberrant form of tuberculosis. Askanazy in 1888 recorded a case of enlargement of the intrathoracic glands and of the glands at the hilum of the spleen. During life irregular pyrexia was present. Post-mortem microscopic examination of the glands showed the characteristic changes of tuberculosis and tubercle bacilli were found in large numbers.

In 1898 Sternberg communicated fifteen cases that had been diagnosed as pseudo-leukaemia, and in which he had been able to examine the tissues microscopically. In one case, diagnosed as pseudo-leukaemia with recurrent fever, miliary tuberculosis was present; tubercles were found in large numbers in the liver and kidneys, and many of the lymphatic glands were caseous. Sternberg advocated the view that all the forms of glandular enlargement with recurrent pyrexia were tuberculous in origin, with the exception of a very few cases in which no evidence of tuberculosis could be found; these he held to be conditions of multiple sarcoma.

Sailer, in the paper already mentioned, quoted three cases of his own, and, referring to cases such as those of Ebstein and Sternberg in the literature, gave an account of a tuberculous disease that had the clinical appearance of Hodgkin's disease with general enlargement of the glands. He stated that some cases were without much fever, a certain number show recurrent fever of two weeks' duration; anatomically the process is tuberculous and tubercle bacilli, as in one of his three cases, may be isolated from the sputum.

In the same year Musser published an article on the subject in the Transactions of the Association of American Physicians. He reported two cases of glandular enlargement with recurrent pyrexia; autopsies were not obtained. In the first case there was no pathological or bacteriological evidence of tuberculosis; the second case was undoubtedly tuberculosis; tubercle bacilli were present in the sputum and the patient died of cerebral meningitis. Musser's conclusions are as follows: 'Hodgkin's disease is in all probability a lymphatic tuberculosis. Fever, recurrent in type, occurs commonly in this infection of the glandular structures. We agree with the conclusions of Sternberg.'

Ruffin, in 1906, while considering the diagnosis of lymphadenoma with relapsing pyrexia, refers to a case of tuberculous adenitis; the patient was a male, aged 30, in whom relapsing fever occurred for a period of twenty-three days. The cervical, axillary, inguinal, and epitrochlear glands were enlarged. The patient reacted to five minims of Trudeau's old tuberculin. Dark brown pigmentation was present on the skin of the cheeks and of various parts of the body. The glands were exposed to the Röntgen rays, and a dermatitis ensued as a result of the application. One of the cervical glands was removed and shown to be tuberculous in nature.

The dispute does not concern the authenticity of the facts reported, but involves the conclusions.   Osler has alluded to the circumstance that Blockley has shown numerous instances in which tuberculosis, such as can only be recognized pathologically, occurs restricted to lymphatic glands; it is met with frequently in young children and in coloured races.   He states that there is a true Hodgkin's disease apart from the variety of tuberculosis described by Sternberg.   Deductions drawn from the cases observed at Brompton Hospital are, it will be shown, entirely in accordance with this view.

Longcope, in Osler's and Macrae's *System of Medicine*, points out that two forms of tuberculous adenitis exist which are difficult to distinguish from Hodgkin's disease: 1. Acute tuberculosis of lymphatic glands; 2. Generalized caseous tuberculous adenitis.   The error has arisen through describing two independent affections under the same name.   For example, in Musser's two cases, one is an instance of lymphadenoma with recurrent pyrexia, the other is a case of tuberculous adenitis with pulmonary tuberculosis.   We have, therefore, two large groups of cases closely assimilating one another in their clinical manifestations, more especially in a recurrent form of pyrexia.   In one the lesion is tuberculous, in the other lymphadenomatous.   In a certain number of cases, chiefly those with external glandular enlargement, pathological examination is alone capable of deciding as to which group they shall belong.

The discussions held at the Annual Meeting of the British Medical Association in 1901, and at the Pathological Society of London in 1902, together with the researches of Reed, Longcope, and Simmons, clearly demonstrate that tuberculosis and lymphadenoma are capable of such pathological discrimination.

A diagnosis of the relapsing form of Hodgkin's disease cannot be made upon inspection of the temperature chart alone, or even upon the clinical picture of glandular enlargement with relapsing pyrexia.   Certain cases of tuberculous adenitis and of pulmonary tuberculosis, either independently or as combined lesions, closely mimic the clinical features of lymphadenoma.

These cases may be grouped under two headings.

It is now proposed to consider the first group of cases.

1. *Cases of Tuberculous Adenitis simulating Lymphadenoma with Enlargement of the External Glands.*

Case VI. G. C., aged 29, married, and by occupation a labourer, was admitted to Brompton Hospital on June 4, 1909, complaining of periods of feverishness and of loss of appetite ; the susceptibility to these attacks dated from an attack of ' influenza ' in December, 1908.

In February, 1909, he noticed that the glands of his neck were enlarged, and became an in-patient of the Westminster Hospital, where one of the glands was removed.   He observed that the glands swelled up and became painful during the feverish periods.

The patient was a well-nourished man; discrete, ' shotty ' glands were palpable in both posterior triangles of the neck and in both axillae. The spleen could not be felt. The ophthalmo-reaction and Von Pirquet's reaction were negative. No tubercle bacilli were found in the sputum.

The temperature chart shows a well-marked pyrexial period, of which three occurred during the patient's residence in hospital. It differs in no way from the types of relapsing pyrexia already given. The pyrexial period occupies thirteen days. There is a gradual rise to a maximum; the highest temperature, 103° F., is attained on the sixth day; on the next two days the temperature is 102·8° F., and then the temperature falls by gradual lysis. Between the pyrexial periods the temperature was not quite normal or subnormal, but varied between 97° and 99° daily. Every tenth day the temperature rose to a maximum of 102° to 103° F. The rise in temperature was accompanied by great enlargement and softening of the affected glands; there was no redness of the skin, but in other respects the glandular condition approximated closely to that described in Case I, and in Batty Shaw's case. Further features of the pyrexial period were chills and cold sweats. In the remission period the glands again became small. The patient refused to have a gland removed for diagnosis, and left the hospital in a very weak state during the third pyrexial period. He died at home two months later. So great was the resemblance of this case to the relapsing type of pyrexia with glandular enlargement in lymphadenoma, that I included it under this diagnosis in the Brompton Hospital Medical Report for 1909.

Through the courtesy of the medical registrar at the Westminster Hospital, I find on inquiry that the gland removed during a pyrexial period in February, 1909, was caseating ; microscopic examination showed that it contained tubercles and giant cells. Thus the correct diagnosis was tuberculous adenitis with relapsing pyrexia.

Case VII. C. P., aged 12, was admitted to Brompton Hospital on August 5, 1910. His symptoms were pain in the left side of the chest of two months' duration. There was nothing noteworthy in the history of past illnesses or in the family history.

On physical examination, nothing abnormal was detected, except that the patient was suffering from enlarged tonsils and adenoids. These were removed shortly after his admission to hospital. There was no sputum; Von Pirquet's reaction was positive.

On September 29 rapid enlargement occurred of the glands in the anterior and posterior triangles of the neck on the right side, and to a lesser extent of those on the left side. The glands were discrete, tender, and did not invade the skin. The other external glands of the body were not enlarged, and the spleen was non-palpable. No primary focus of infection was discovered in the mouth or pharynx.

The temperature chart shows a typical relapsing period, terminating by lysis, and lasting from September 24 to October 4. The maximum temperature was 102° F.

The glands diminished in size towards the close of the pyrexial period, and by November 2 they were small, hard, and the skin was freely movable over them. The opsonic index to the tubercle bacillus was: 1·06 before massage of glands, 1·43 after massage of glands. No ill effects followed the injection of 1/50,000 mg. of tuberculin (T.R.). The blood-count was normal.

On November 12 one of the cervical glands on the left side was removed under local anaesthesia. On microscopic examination it was found to be tuberculous. Another pyrexial period occurred from November 26 to 29. The temperature in the interval between the periods showed moderate pyrexia (average evening temperature 99° F.).

The patient was discharged improved on December 15.

Case VIII. E. A., aged 38, single, by occupation a painter, was admitted to Brompton Hospital on June 13, 1910.   The patient was sent in as a case of lymphadenoma, the cervical glands being enlarged and the right and left upper lobes consolidated.   The temperature was raised, and it was noted that the glands varied in size to a certain extent with the height of the pyrexia.   Tubercle bacilli were present in the sputum, while microscopic examination of an excised gland showed that it was definitely tuberculous in nature.

Case IX. H. D., aged 16, errand boy, was admitted to Brompton Hospital on August 3, 1910.
This case showed a condition of advanced pulmonary tuberculosis, with uniform enlargement of the external lymphatic glands.   On microscopic examination the glands were found to be tuberculous.   Tubercle bacilli were present in the sputum.
The patient was removed, at his friends' request, from the hospital on September 4, 1910.   He died at home ten days afterwards.

Case X.   W. N., male, aged 18, by occupation a laboratory assistant, was admitted to Brompton Hospital on October 31, 1910.
The patient had tuberculous adenitis of the external lymphatic glands. There was no pulmonary lesion.   Mitral stenosis was a complication.

Cases of tuberculous adenitis or of chronic pulmonary tuberculosis with enlargement of the spleen are rare.   That they occasionally occur is shown by the following case :—

Case XI.   E. A. F., male, aged 20, a park gardener, was admitted to Brompton Hospital on October 8, 1902.   His illness dated from an attack of pneumonia at the age of 16.   The onset was with haemoptysis.
The physical signs in the chest were those of advanced chronic pulmonary tuberculosis.   Tubercle bacilli were present in the sputum.   There was no enlargement of the superficial glands.   The spleen was enlarged and could be felt extending from the left costal margin to one inch below the umbilicus.   The patient professed to have experienced tenderness in the organ two years previously.   There was no evidence of amyloid disease.   It was noted that the spleen varied in size with the degree of pyrexia.
The patient was discharged, improved, on January 3, 1903.   He was re-admitted on October 21, 1908.   The signs of pulmonary tuberculosis had greatly extended.   Small discrete glands were palpable on the right side of the neck, and in both axillary and inguinal regions.   One of the glands in the inguinal region was excised and its tuberculous nature demonstrated.   The spleen reached to about half an inch below the level of the umbilicus.   The blood-count showed a severe grade of anaemia.
On December 14, the temperature being then 101°, the patient complained of acute pain over the splenic region.   This attack passed off in the course of twenty-four hours, but it was noted that the spleen had extended to one and a half inches below the umbilicus.   The patient left the hospital on January 5, 1909, and has since been lost sight of.
A similar case, except that relapsing pyrexia was present, and in which the patient died of tuberculous meningitis, is recorded by Musser as one of Hodgkin's disease.

The last four cases, then, in the character and distribution of a tuberculous lymphadenitis, closely simulated the glandular enlargement of lymphadenoma.
If a relapsing type of pyrexia had been present, as occurred in the first and

second of the six cases, they might all have passed as cases of lymphadenoma with relapsing pyrexia, the pulmonary lesion in Cases VIII, IX, and XI being considered as a complication.

Microscopic examination of the glands alone sufficed to avoid this error of diagnosis.

2. *Cases of Chronic Pulmonary Tuberculosis with a Relapsing Type of Pyrexia.*

Cases of chronic pulmonary tuberculosis with a relapsing type of pyrexia are occasionally met with. They form about 1·2 per cent. of all cases of chronic pulmonary tuberculosis, the six cases here noted being collected from an examination of 500 cases of the disease. I have excluded all the cases where the exacerbation of temperature was presumably due to some complication, such as an attack of catarrh, tonsillitis, or influenza ; hence the cases under consideration are uncomplicated cases of chronic pulmonary tuberculosis. All the cases were undergoing treatment in Brompton Hospital.

Case XII. C. P., male, aged 23, clerk, was admitted to hospital on September 11, 1906. His illness commenced in October, 1905, with an attack of pleurisy.
On admission. The patient was pale and emaciated. The note over the right lung was impaired at apex and expiration prolonged. Infiltration of upper lobe of the left lung and of the apex of the lower lobe. Tubercle bacilli were present in the sputum. No glands were palpable. The spleen was not enlarged. He was discharged on November 26, unimproved, with active disease in the left lung and with the disease advancing in the right upper lobe.
The temperature chart showed a first period of moderate pyrexia for seventeen days, in which the temperature was normal or subnormal, with occasional evening swings to 99° F. The first pyrexial period lasted eleven days : the temperature gradually rose, and on three occasions touched 100·8°. After this the temperature fell by lysis. There was a swing up to 100° at the close of the pyrexial period. The temperature then fell to 98°. Then followed an interval of apyrexia for seven days ; the temperature was normal or subnormal throughout. The second pyrexial period lasted seven days ; the ascent was gradual but more rapid than the first period. The highest temperature of the period, 101·8°, was recorded on the second day. Lysis occupied five days. Next followed an apyrexial interval of twenty-five days, and after that a third pyrexial period of eleven days. This was the most striking of the three periods. Here again the highest temperature recorded, 104·4°, was reached on the second day. The patient left hospital before lysis occurred, the last recorded temperature being 101·5° F. The chart resembles that of a case of lymphadenoma with relapsing pyrexia.

Case XIII. W. C., male, aged 21, brass-finisher, admitted March 9, 1900. The physical signs were those of consolidation of the right upper lobe, with a certain amount of softening. Tubercle bacilli were present in the sputum. No enlargement of the glands or spleen was found. The patient was discharged, improved, on June 2, 1900.
The chart shows that the patient was admitted during a pyrexial period. At the end of six days the temperature fell by lysis. Towards the close of the seventh day a second pyrexial period commenced, which lasted for four days. For fifteen days a period of moderate pyrexia ensued, the temperature subnormal in the morning, rising at night to 99° F., or one or two degrees over this number

occasionally. The second pyrexial period was of four days' duration; next came an apyrexial interval of one one day, followed by a fourth pyrexial period of seven days. Twelve days' interval ensued, during which the temperature was for the most part normal. The fifth pyrexial period lasted for three days.

After five days' moderate pyrexia the sixth pyrexial period commenced and lasted for eight days. The temperature was continuously raised; the highest temperature recorded, 103° F., occurred in this period. After three days' apyrexia a short pyrexial period of two days took place, and from this up to the discharge of the patient the temperature was one of moderate pyrexia.

Case XIV. A. J. P., aged 46, male, ticket-collector, admitted July 22, 1903. The physical signs were those of consolidation of the right upper lobe. Tubercle bacilli were found in the sputum. He gained in weight, his cough disappeared, and he was discharged on October 19, 1903, greatly improved. The temperature chart showed two well-marked periods of pyrexia. In the intervals the temperature was normal with occasional exacerbations to 99° F.

Case XV. F. T., male, aged 35, draughtsman, was admitted on August 16, 1907. The physical signs were those of consolidation of the right upper lobe. Tubercle bacilli were present in the sputum. The patient was discharged, improved, on November 15, 1907.

The temperature chart shows three well-marked pyrexial periods. In the intervals the temperature was for the most part normal. During the pyrexial periods adventitious signs increased in amount in the affected area at the right pulmonary apex.

Case XVI. W. H. S., male, aged 31, engineer, was admitted on March 11, 1903. The only history of past illness was that at the age of eighteen the glands in the neck were swollen. The pulmonary physical signs were those of infiltration of both upper lobes; in addition, a well-marked pleural friction rub could be heard in the right axilla. This had disappeared by April 2. Tubercle bacilli were present in the sputum. The patient was discharged on April 4, 1903.

The temperature chart showed a temperature on admission of 97° F. Two well-marked periods of pyrexia are displayed; the first one occupied two days, the second three days. In the intervals and after the second pyrexial period the temperature was normal.

Case XVII. J. S. A., aged 29, cabinet-maker, was admitted on June 27, 1910. The physical signs showed that the upper lobes of both lungs were infiltrated, the signs of tuberculosis being less marked in the left than in the right lung. Tubercle bacilli were present in the sputum. From August 2 to August 4 the sputum was tinged with blood. He was discharged, improved, on September 26, 1910, but the signs at the apex of the right lung had progressed to the stage of consolidation.

The temperature chart is one of relapsing pyrexia, two marked periods being recorded. 102° was the highest temperature reached in the first period, and 103° in the second. Lysis is prolonged, especially in the second period, while in both cases there is the usual drop to a subnormal level at its close. Between the periods the temperature is continuously normal or subnormal, with the exception of an evening exacerbation to 99° on two occasions. At the height of the first period, on July 4, a herpetic eruption appeared on the lower lip and an increase of adventitious sounds in the right lung was noted. With the advent of the second bout of fever a pleuritic rub was heard over the third rib in the left axillary line. This disappeared in about ten days' time.

Case XVIII. The following case is one in which a definite diagnosis between pulmonary tuberculosis and lymphadenoma with relapsing pyrexia could not be made :—

H. T. R., aged 43, male, flower-hawker, was admitted on December 18, 1908.

He had pleurisy with effusion on the right side in June, 1908, for which he was twice aspirated.

Physical examination revealed dullness with weak breath-sounds at the base of the right lung. There was some slight impairment of the percussion note at the pulmonary apices.

The patient on admission (the temperature being normal) had some pleural friction at the angle of the right scapula ; this disappeared in the course of a week or two. No tubercle bacilli were present in the sputum (three examinations). The opsonic index to the tubercle bacillus was : 1·0 before exercise ; 1·2 after exercise. The patient did not react to 5 mg. of Koch's old tuberculin. Von Pirquet's reaction was slightly positive. The patient was discharged, improved, on March 19, 1909.

The temperature chart shows a typical relapsing form of temperature with five pyrexial periods. In the interval the temperature was subnormal or normal with occasional exacerbations to 99° F. The two first pyrexial periods are the most prolonged and marked. The highest temperature was 103·8° F. in the second pyrexial period.

The evidences for the case being one of pulmonary tuberculosis are the onset with pleurisy, the slight impairment of the percussion note at the apices of the lungs, the positive Von Pirquet reaction, the absence of chills and sweats or enlargement of the spleen during the pyrexial periods, and the improvement manifested by the patient. On the other hand the absence of tubercle bacilli in the sputum, and, possibly, the normal opsonic index to the tubercle bacillus, suggest that the case was one of lymphadenoma. As already remarked, stress must be laid upon the improved condition of the patient on discharge, which is much more in favour of pulmonary tuberculosis.

These six cases are adduced for the purpose of showing that a definite relapsing pyrexia is occasionally found associated with chronic pulmonary tuberculosis.

In the first case the pulmonary disease advanced ; in the second softening was present ; the third case did not show any variation, but in the fourth case the adventitious sounds increased during a pyrexial period, while pleurisy occurred in the fifth and sixth cases.

Hence, without speculating as to whether these periods of pyrexia are due to an intermittent discharge of toxins or the like, it is permissible to conclude that they indicate an increase in the activity of the tuberculous process in the lung. The intervening period of moderate fever or apyrexia does not, as is shown by Case XII, of necessity imply a subsidence, but rather a lesser degree of activity.

Conclusions.

A clinical and pathological description of lymphadenoma with relapsing pyrexia has been given.

Two chief types are distinguished :—

1. In which the external and internal lymphatic glands are involved.
2. In which the internal lymphatic glands are solely affected.

This description has been primarily based upon the five cases of lymphadenoma reported in this paper. In each instance the pathological aspect of the case was considered and the clinical diagnosis of lymphadenoma was verified during life by the excision and examination of an affected gland. It must be borne in mind that it is only within the last seven years that a clear description of the histology of lymphadenoma has been furnished to us.

These five cases are found not only to harmonize in their clinical features with one another but also to resemble certain other cases in the literature, so that finally a total of thirty-two cases was tabulated (comprising the five recorded cases together with twenty-seven cases collected from the literature).

These thirty-two cases have furnished the data for the general account of the disease here given.

In the second place, a large amount of attention has been paid to the inter-relation of lymphadenoma and tuberculosis. Investigation showed that such a relation also exists between the special variety of lymphadenoma and tuberculosis.

Cases of tuberculous adenitis with relapsing pyrexia are recorded in the literature, and reference is made to them from the time of Morgagni onwards.

With a view to emphasizing the similarity of such cases to the first type described in this paper (in which the salient feature is enlargement of the external lymphatic glands), seven cases of general tuberculous adenitis were communicated, in two of which the temperature was of the relapsing type, and which were only distinguishable from lymphadenoma by microscopic examination of the affected glands.

In the practice of the Brompton Hospital my attention had been drawn to the circumstance that a certain proportion of the cases of pulmonary tuberculosis had a relapsing type of pyrexia, and further that such cases, more especially those with the disease in an early stage, closely mimicked the second type of lymphadenoma with relapsing pyrexia, that type in which the internal glands are alone involved.

In support of this statement six cases of pulmonary tuberculosis with a relapsing type of pyrexia were described, and one case in which the differential diagnosis could not be made with any certainty.

Finally, it may be pointed out that the question of the recognition of this special variety of lymphadenoma is not merely one of academic interest. The prognosis of the disease alone makes the subject of importance: its characteristics are of value in differentiating it from other maladies. Especially is this the case with reference to glandular and pulmonary tuberculosis.

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CASE 1.   Gland excised from the cervical region.   Lymphadenoma, intermediate stage (cell hyperplasia with proliferation of the connective tissue).
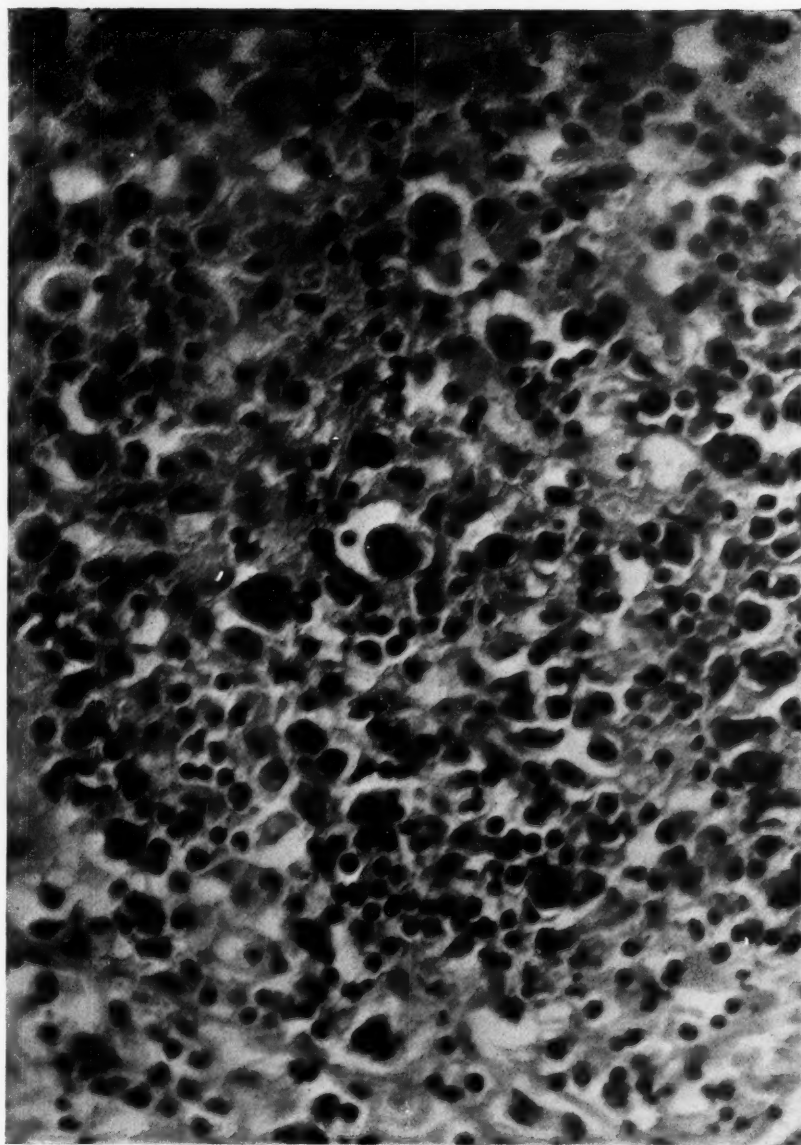
CASE 2. Gland excised from the groin. Lymphadenoma (hyperplasia of the cellular elements with proliferation of the reticulum. Eosinophils numerous).
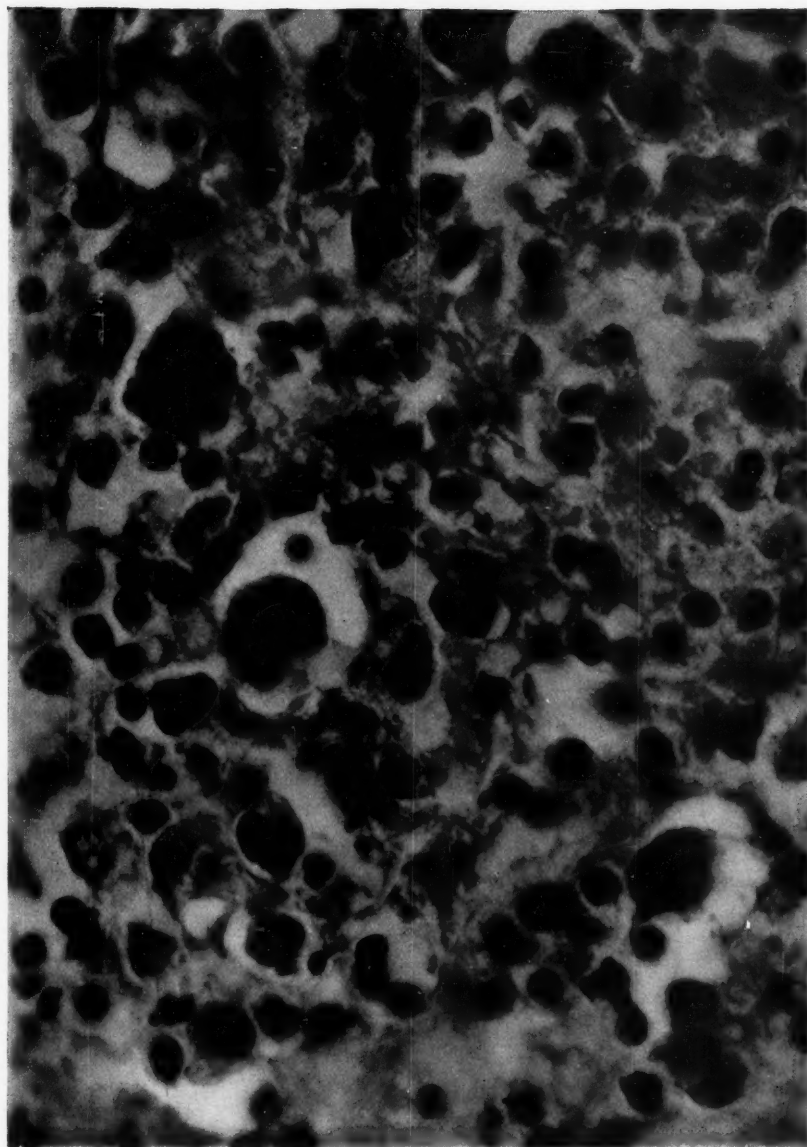
CASE 2.   Gland excised from the groin.   Lymphadenoma.   (Similar to Plate 6, but seen under a much higher power. The giant-cells are well displayed and form a prominent feature of the section.)

CRITICAL REVIEW

KALA AZAR AND TROPICAL SORE

By WILLIAM B. LEISHMAN

KNOWLEDGE of the group of diseases caused by parasites of the genus *Leishmania* has made great advances during the last three or four years and, although finality is very far from having being attained in respect of any one of them, it may be useful to take stock of the present situation in order that attention may with greater profit be concentrated on the points which remain obscure. Such a critical summary may also be of service to those who are working on the subject, for the further reason that much if not most of the recent work on the subject is from the pens of investigators in other countries and is published in many journals and in many tongues, so that such workers, unless in close touch with a good library, may find great difficulty in obtaining the latest information. The literature has grown so rapidly of recent years that it is no easy task to keep touch with it, and in the present case no claim can be made that an exhaustive study of it has been accomplished, although the list of references may appear a lengthy one. It is felt, however, that any omissions in this connexion may be excused, since the Managing Committee of the Sleeping Sickness Bureau have decided to publish a Bulletin of the *Leishmania* diseases, on the lines of the Bulletin of Sleeping Sickness, and it is intended that the first number, which will appear before long, shall contain a complete bibliography up to the present date.

It is only eight years since the discovery of the parasites, and up till that time few except tropical physicians were familiar with the names even of kala azar and of tropical sore, as distinct clinical entities. Once the parasites were recognized, however, knowledge of these diseases rapidly extended, and one of the practical results of this has been the realization that kala azar is by no means limited to Assam but is widespread throughout the globe, and, further, that the tropical sores described in so many countries under innumerable names are alike in respect of infection with parasites of the *Leishmania* group. What is still more of interest at the present moment is the fact that a form of kala azar has been found to be more or less frequent in countries bordering the Mediterranean, and the numerous cases which have been detected in Italy, Greece, Portugal, and elsewhere have proved that it can no longer be considered a disease of interest solely to those working in the tropics. Again, it has been

abundantly shown that the terrible mortality of the Indian form of kala azar has its counterpart in that found in Africa and Europe, and humanity as well as science demands the strenuous investigation of the aetiology, treatment, and prevention of this deadly scourge.

The unity of the various forms of tropical sore, though of scientific interest, is of less practical importance in view of the benign character of this affection ; however, a form of ulceration which is usually altogether uninfluenced by treatment, and which only tends to heal spontaneously after many months, is of sufficient annoyance to justify almost equal zeal in investigations directed to its understanding and mastery.

In dealing with the subject, it is proposed to act on the assumption that the earlier work on these diseases is familiar to the reader ; every textbook on tropical diseases gives full information on the subject which it appears needless to recapitulate. The article is therefore confined to a summary of the work which has appeared during the last four years and to comments upon some of this work, where comment falls within the competence of the writer.

It was originally intended to deal only with the systemic disease kala azar, but, for many reasons, into which it is unnecessary to enter, it has been thought better to deal with the whole group, to which the somewhat cumbrous name of Leishmaniosis has been given—in conformity with trypanosomiasis, piroplasmosis, &c. At the outset, therefore, lies the question of how many forms of *Leishmania* are recognizable and how far any given classification is tenable. It may be said at once that no classification can be accepted as final at the present moment. There are, however, two well separated diseases, the one a generalized systemic infection, almost invariably fatal, the other a localized cutaneous disease, invariably benign. These are respectively, kala azar, associated with the presence of *Leishmania Donovani*, Laveran, and tropical sore, or *bouton d'Orient*—to give it only the names most generally employed—which is attributable to *Leishmania tropica*, Wright. These two diseases would appear to be as widely separated clinically as would be possible, and yet, even here, it has been suggested many times that we have to do with one and the same parasite as causative agent. The possibility of both groups of disease being due to one parasite cannot be said to be altogether excluded, although it is extremely improbable. The difficulty lies in the fact that the two parasites, *Leishmania Donovani* and *L. tropica*, are indistinguishable morphologically, and it is not at present possible to detect any constant and definite distinction either in their pre-flagellate or their developmental forms.

While this is the case with kala azar and tropical sore, it is naturally a still harder matter to decide in how far these two diseases might themselves be further subdivided, and it need only be added here that it is convenient to classify the group, for the purposes of this article, into three diseases, namely, Indian kala azar (*L. Donovani*, Laveran), infantile kala azar (*L. infantum*, Nicolle), and tropical sore (*L. tropica*, Wright).

I.

Indian Kala Azar. *L. Donovani*, Laveran.

Although this disease was the first in which the Leishmania parasite was demonstrated (in 1903), and has been the subject of much careful research and observation, there has been little real advance in our knowledge within the last few years. As could be anticipated, diffusion of knowledge of the appearance of the parasite and of the methods necessary for its demonstration have led to the discovery of the disease in many parts of India and the surrounding countries where its existence had not been suspected. In the original focus of the disease, Assam, there has been a marked diminution of the annual number of deaths, which have fallen from 6,315 in 1900 to 1,703 in 1909, so there would appear to have been a gradual decline in the virulence of this prolonged epidemic. History tells of similar epidemics in various parts of India which may very probably have been kala azar, and which similarly exhausted themselves and disappeared from the country or district. On the other hand, endemic foci have been found in numerous parts of India, and in other Asiatic countries lying to the west and the east of India, which furnish a formidable total of cases, and from which, it may be assumed, there is an ever-present danger of epidemic spread, similar to the Assam epidemic. In India itself cases have been reported which were apparently contracted in Nepal and at Naini-Tal, while Prashad states that the disease is very common in Patna, ninety-four cases having been admitted to Bankipore General Hospital in one year. Incidentally, this last series serves to illustrate the difficulty of determining age and sex incidence in the disease; all of these ninety-four cases were males, but Prashad points out that this is solely due to the fact that children and female patients are rarely or never seen by a practitioner, owing to caste prejudices.

Precise figures as to the incidence of the disease in India as a whole are not forthcoming, and even in those districts, such as Assam and Madras, where figures may be collected from the Sanitary Reports, it is only the cases which have come under the notice of medical practitioners able to recognize the disease which are recorded; there can be little doubt that these form but a fraction of the whole, the large majority being unrecognized, and that many fatal cases are still recorded as malaria, dysentery, &c. The future will bring improvement in this, and will no doubt make wide additions to the areas known to be infected, as well as to the number of sufferers.

As regards age incidence in India, the earlier views that the disease may attack any age but shows a preference for young adult life are supported by recent observations, but in this respect and also in respect to sex incidence there is, as has been said, little definite information, and any conclusions on these points must be accepted with reserve.

Both in Calcutta and in Patna the number of cases has been greater in Hindoos than in Mohammedans, but here again precise information is lacking, and all that can safely be said is that no race or creed appears to be exempt from attack. Europeans contract kala azar but rarely, but the enormous disproportion

between them and the natives must be borne in mind ; when they do contract it they certainly exhibit no evidence of a higher immunity, since it is almost invariably fatal in such soldiers as have been invalided to England with the disease.

The distribution of the disease outside India itself at once brings one face to face with the problem of the identity or non-identity of the Indian disease with other forms of kala azar, but assuming that all cases of the disease occurring in Asia are due to the same parasite, we do not find any great extension of the areas already known to be infected in Syria, Ceylon, Burma, Indo-China, and China itself.   Several endemic foci in China have, however, attracted attention, for instance Peking and the upper part of the Yangtse Valley, while cases have been found by Elders and others in the Dutch East Indies, both in natives and in temporary residents.

A notable feature of this side of the question has been that, once a case has been found in a new locality, and once the attention of the local practitioners has been drawn to its occurrence, the disease is soon found to be far from rare, and, further, one which has long been familiar both to the inhabitants and the medical men, although its true nature had not been suspected.   This being so, it is highly probable that even now but a small number of the infected countries have been identified, and that some time must elapse before we shall be in a position to assign definite geographical boundaries to this form of kala azar.

Morphology.   Little falls to be added to the very full details of the morphological characters of *Leishmania Donovani* which were published by earlier workers and have been abundantly confirmed since.   The intracellular form, or as it is called the 'Leishman-Donovan body', is remarkably constant in form and shape, and close examination of many specimens, derived from various countries and from different patients, has not disclosed any fresh features which might serve towards a differentiation of species.   Fission forms have been encountered free in the blood, as well as in the cells of internal organs, but no confirmation has yet been recorded of Elders's observation in a case of a Madras woman, apparently infected in Sumatra, of a flagellated parasite in the peripheral blood.   (In a later paper Elders describes another case in which the blood contained a new parasite akin to *Haemoproteus*.)   It is indeed remarkable that such have never been seen by any other observer, in view of the wide distribution of the parasites in the body and the very varying conditions, as regards environment, which they must from time to time encounter.   Bousfield comments on the occurrence of parasites in the liver or spleen of cases in the Sudan in which the two chromatin masses appeared of nearly equal size, and suggests the possibility of these being sexual or conjugation forms ; but this appears unlikely, and parasites are not infrequently seen where such an enlargement of the centrosome is obviously an early stage of simple fission of the parasite, while others are with equal clearness degeneration stages.

Cultures and cultural forms.   The first successful cultural experiments of Rogers were soon repeated and confirmed by Chatterjee, by Leishman and

Statham and, since then, by many others, and successful development of the parasites into flagellate form is usually to be obtained by keeping citrated splenic blood under aerobic conditions at a temperature of 22°–25° C. Success, however, is by no means invariable, even when the parasites are fairly abundant and when the material is derived directly from a splenic or a hepatic puncture and not obtained post mortem. Rogers's recommendation that the cultures should be acidified by the addition of a small quantity of citric acid have not been confirmed, and there does not appear to be any advantage in such a procedure ; indeed, in a case in which the writer took the opportunity of testing this point, growth and development were more free in the cultures to which no citric acid had been added.

Great interest attaches to the capacity of the Indian strain of kala azar to develop in Novy-McNeal medium. Those who have attempted this in India have failed to get development into flagellate form, whereas, in the case of *Leishmania infantum*, rapid and abundant growth occurs in this medium and failure is usually recorded with citrated splenic blood. This cultural difference is usually held to be one of the more important points in support of the view that we ought to recognize the two as distinct species, and the difference appears to be constant, since it has been reported by numerous workers who have tried both cultural methods with the strain occurring in their own districts, Indian or Mediterranean, respectively. At the same time, the writer has succeeded on one occasion in securing flagellate development in Novy-McNeal medium of parasites derived from a spleen puncture of a soldier in the military hospital at Millbank who had contracted the disease in Bengal. As far as he knows, however, this is the only positive result, so it stands alone against many failures in most careful and capable hands. The point is one of considerable importance, and further work with simultaneous experiments with each strain is much wanted and will doubtless be forthcoming ere long.

The details of the development of the parasites in cultures and the structural characters of the flagellated organisms have formed the subject of close study by many workers, but no new facts of importance have been brought to light. The comparisons made between the flagellated forms of *L. Donovani, L. infantum,* and *L. tropica* will be mentioned again, but it may be said here that differences of a specific character, if they exist at all, are very slight, and that the well-known polymorphism of these cultural forms adds greatly to the difficulty of determining their genuine character.

Animal experiments. So far there is no record of the successful transmission of Indian kala azar to an animal, and experiments with this strain at home have also failed. This failure is remarkable in view of the successful transmission of the Mediterranean form to dogs and monkeys, and also, though in mild form, to rabbits, rats, mice, and guinea-pigs. If further experiments, which are greatly to be desired, are found to have similar negative results, this would assuredly constitute a striking difference between the two, but the question cannot be said to have been settled, in view of the small number of the experi-

ments recorded in India by Patton, Christophers, and Donovan. Nicolle's inoculation experiments on dogs and monkeys with the infantile strain have been positive in the majority of instances, but Italian and French investigators have not been able to secure infection in anything like the same proportion of animals. This would indicate that the conditions favouring successful experimental inoculation may show considerable variation, even when one is dealing with what appears to be the same strain of virus. This being so, it would be necessary to repeat Nicolle's experiments on a much larger scale in India than has been done, in different localities and with different species of dog and monkey, before we are able to accept as a fact that the Indian form of kala azar is not transmissible to these animals. Here, too, a ready solution of the problem would appear possible if only an Indian case was available for investigation in M. Nicolle's laboratory at Tunis, or one of his infantile patients could be transferred for a time to Madras or Calcutta.

Pathological anatomy. The numerous and exhaustive accounts which are already on record of the distribution of the parasites in the body and the changes which they produce in the tissues leave little room for fresh observations, but Rogers has described an unusual form of cirrhosis of the liver which he believes to have been caused by *L. Donovani*, which was present in abundance in the organ in the particular case, that of a Hindu. The cirrhosis was of a peculiar intralobular type and showed an even distribution throughout the organ, whose surface remained quite smooth. He has noted this form of cirrhosis to be commoner in Bengal than that due to malaria, and believes that it has often been wrongly attributed to the latter disease. A form of splenomegaly associated with hepatic cirrhosis has also been described by Day and Ferguson as endemic in Egypt, and their account of the symptomatology corresponds very closely with that of Indian kala azar ; they were, however, unable to detect any parasites in their cases.

Symptomatology. The clinical signs of kala azar, as it is met with in India, are now fairly well known and, taken together, give a picture which is very distinctive, so much so that in the majority of cases in which the disease is well established it is possible to be fairly confident of the diagnosis, even in the absence of a demonstration of the presence of the parasites. The character of the fever, the enlargement of the spleen and, in lesser degree, of the liver, the transitory oedemas and the leucopenia, together with other features which need not be recapitulated, go to make up a picture which, to say the least, is very suggestive. The writer has known of numerous cases diagnosed by brother officers on this congeries of symptoms alone which, on being subsequently submitted to the test of splenic or hepatic puncture, have been verified by the demonstration of the parasites, and this in some instances in localities where the existence of the disease was unsuspected.

The earlier descriptions of the symptomatology stand good at the present moment and have been abundantly verified. It may be added that the symptoms of the Mediterranean form, due to *L. infantum*, are almost identical and the

small points of difference which certain observers have noted will be commented on in dealing with this form.

Much of the literature which has appeared in recent years on the subject gives careful and accurate details of the symptomatology of the cases which came to the authors' notice, but it is not possible to find in these descriptions any common symptom of new diagnostic importance. The character of the fever assumes a large part in these clinical accounts, and many of the lengthy charts of the cases are published *in extenso*; all serve to emphasize the fact of the very varied and irregular course which the temperature curve may assume. Cases could be divided into certain categories according to the main features of the temperature oscillations, but any description or analysis of these would occupy much space without serving any very useful purpose. The frequent occurrence of a double rise of temperature within the twenty-four hours, originally noted by Rogers, has, however, been confirmed in many cases, and Chatterjee states that cases of fever showing this peculiarity are not uncommon in Bengal; he has seen ten cases in the last five years in which the temperature took this form of a double quotidian type, there being two rises in twenty-four hours, each preceded by a definite rigor and separated by an interval of complete apyrexia. These cases he now believes to have been early cases of kala azar, and, indeed, in one of them the parasites were subsequently demonstrated, while another occurred in a family in which there were present two undoubted cases of the disease.

Several authors mention the fact that the spleen is not invariably enlarged— Donovan says that this is the case in about 2 per cent. of the Madras cases—and the rapid variation in the size of this organ, previously noted, appear a not uncommon feature. Elders, describing the case of a Javan at Sumatra, mentions a swelling of the lymphatic glands of the neck, axilla, and groin, but he does not appear to have attempted to prove the presence of the parasites by puncture of these glands, and the case may have been one of the new disease he thinks he has discovered.

The attainment of certainty of diagnosis still rests on the demonstration of the parasites, and in the enormous majority of the cases which have been recorded this has been accomplished by spleen puncture and the staining and identification of the parasites in the films made from the spleen juice. The question of spleen puncture as a diagnostic method is considered later; but reference must be made here to Donovan's experience. He states that he has now abandoned spleen puncture on account of its dangers, and relies on prolonged examination of films of the peripheral blood, which has given him 93.22 per cent. of positive results. No other observer has had anything approaching this percentage of success, and the majority still rely upon spleen puncture. Hepatic puncture is generally recognized as being less satisfactory, since parasites may not be detected in the films although post-mortem examination at a later date may prove them to have been present in abundance in the liver.

Donovan states that he thinks he is able to detect a change of type in the

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disease, as he meets with it in Madras, and that it appears to be becoming some-
what milder than formerly, but he speaks guardedly and has not produced any
evidence in support of this idea.   From all one can gather from the reports
of Indian kala azar in general, it appears that recovery is certainly possible, but
that the death-rate is well over 80 per cent.

Treatment.   In so desperate and intractable a disease it is natural and proper
that a great variety of drugs and methods of treatment should be employed, in
the hope of avoiding or at least delaying the almost inevitable end.   The recent
remarkable successes of chemotherapy encourage the hope that success may yet
attend the search for a successful drug, but one must with regret conclude that
the Indian form of the disease has not yet been conquered.   It is sad to find so
many articles concluding with a summary of the many methods and drugs
employed and almost always ending with the statement that none of them
appeared to have any pronounced beneficial effect.   Much was hoped from
atoxyl, especially in view of the recoveries which Manson recorded as follow-
ing on the prolonged administration of very small doses, but his success has
not been repeated in India.   Bramachari, however, says that atoxyl has given
him good results when exhibited in doses of 0·9 grm. every 7–10 days for a few
months, but adds that he does not think that its beneficial effect is produced by
any direct action on the parasites.   Several other observers, however, have tried
this drug extensively and abandoned it as useless.   Arsenic, mercury, and
antimony, in various forms, have given equally unsatisfactory results.

Fuchsine, of which Donovan formerly thought well, he now abandons, and
a similar failure has resulted from his use of thymol.   Ensor tried senega on
some of his Sudan cases and was encouraged by his earliest attempts, one of his
two first cases recovering after the development of a leucocytosis.   He was led
to this drug by its richness in saponin, which is said to be very destructive
of protozoal life.   His subsequent cases, however, have not borne out his hopes,
and other officers who tried its effect in other countries had no success.

The failure of quinine in the disease has come to be looked upon as a sign
of almost diagnostic value, and recent reports are practically unanimous in
recording its uselessness, when given by the methods customary in malarial
infection.   A hopeful note has, however, been struck lately by Muir, who has
used it with a view not so much to any specific action on the parasites as to the
production of serous effusion and subsequent leucocytosis by means of hypodermic
inoculations.   By his method he claims to have reduced the mortality of the
disease in a striking manner, especially in cases in which infection was com-
paratively recent.   Since his experience of the disease is exceptionally large—
he states that as many as 700–800 cases may be seen in a single week at Kalna—
his method may be given in more detail.   He employs a solution of the following
formula: Quin. sulphat., 32 gr.; Acid sulphur. dil., 1 dram; Aqua destill.,
4 drams.   From 20 to 90 minims of this solution are injected into the *latissimus
dorsi* in adults or into the gluteal region in children.   It causes great pain, but
this he modifies by a previous injection of cocaine, the needle being left *in situ*

for two minutes and then the quinine solution injected through it. An effusion of lymph occurs and this is followed by a polynuclear leucocytosis, a fall in the temperature, and a diminution in the size of the spleen. He repeats the injections as soon as or before the swelling has subsided.

Muir notes, as have others, that cancrum oris has sometimes been followed by recovery, although it is one of the common terminal affections of the disease, and he has seen other cases which suggest that any process in the body, whether septic or not, which tends to produce effusion of lymph and a leucocytosis tends to check kala azar. In this connexion he mentions two interesting observations of indigenous native treatment of the disease. In Syria, where it is common, the natives often employ a dirty seton, inserted over the region of the spleen, and in Bengal there is a custom of producing an ulcer of the skin by rubbing into a scarified surface a powder obtained by incinerating the core of the jack-fruit.

Prashad records three recoveries after subcutaneous injection of phagocytin, but has had no success from soamin or from the hypodermic injection of the hydrochlorate of quinine.

In considering the results of recent treatment of the Indian form of the disease, it is very noticeable that in many cases in which improvement or recovery has followed some line of treatment, a polynuclear leucocytosis has been one of the features, and a not infrequent portion of a successful treatment has been the production of severe or prolonged counter-irritation, usually over the region of the spleen. As regards the latter, the only case of recovery which the writer has seen in a soldier was in a man who suffered from a severe and intractable X-ray burn over the liver. Counter-irritation and the production of a leucocytosis would appear, then, to be desirable aims in any future system of treatment.

Aetiology. It is regrettable that we still lack precise knowledge of the mode of infection in the Indian form of the disease. The rapid advances in connexion with the aetiology of the Mediterranean form gave reason to hope that similar progress, confirmatory or other, would be made in India, but this has unfortunately not been the case.

Two views have been advanced as to the transmitting agent of the parasite, that of Rogers, who believes that the common bed-bug of India, *Cimex rotundatus*, Signoret, is the agent concerned, and that of Donovan, who suggests a large, plant-feeding bug, which is an occasional blood-sucker, *Conorrhinus rubro-fasciatus*, de Geer. Rogers's views, which were chiefly founded on general epidemiological grounds, have received some support from Patton and from Christophers, and each of these, especially the former, has endeavoured by feeding experiments to solve the problem. The principal difficulties in connexion with satisfactory feeding experiments, which are essential for definite proof of connexion between a suspected insect and a disease, are first, that so few cases are encountered in which parasites are present in the peripheral blood of the patient in numbers great enough to make infection of the insect probable or possible; second, that in India no animal has been found which is susceptible to the disease. A further difficulty, and one which bulks largely in all such experi-

mental problems, is the need for prolonged and systematic study of the natural parasites of the suspected insect or acarian. This naturally adds greatly to the difficulty of determining whether any parasites found in a bug or *Conorrhinus* which has been allowed to feed on a case of kala azar are developmental forms of *Leishmania* or flagellates of another kind.

Patton, however, whose careful studies of the normal flagellates of bugs and other animals have rendered him especially well equipped for such work, is strongly of the opinion that the bed-bug is the true intermediate host and transmitting agent, and in some of his experiments he was convinced that the parasites ingested from the patient's blood had undergone development into flagellated form. These results, however, were only obtained in a few instances, and the confirmation which is desirable in such experiments has not yet been recorded. On the other hand, Donovan, who attempted to confirm Rogers and Christopher's work by feeding bugs on some of his cases at Madras, failed to obtain evidence in support of the theory of bug-transmission. He also made a search in the gut contents of a large number of bugs, collected either in the hospital itself or in the part of Madras City in which the disease is endemic, without encountering any parasites which he could identify as *Leishmania*, either in its flagellate or non-flagellate form.

Against the bug theory is the observation which has been put on record by several observers that careful search and inquiry led them to believe that they had been able to exclude the possibility of bug infection in particular cases, but negative evidence of this character is naturally of minor value. The history of malaria is full of instances in which the presence of *Anopheles* was apparently excluded in a district in which subsequent search was successful.

The *Conorrhinus* theory of Donovan rests on somewhat slender evidence and, as far as the writer is aware, has not been made the subject of experiment by any other worker.

Since Nicolle and his colleagues have shown that *L. infantum* is a natural disease of dogs, and Pianese and others have practically proved the transmission of this disease from dog to dog and from dog to man by the agency of the dog-flea, *Pulex serraticeps*, it is in this direction that further and more extended investigation in India is so urgently called for. Up to the present, the researches of Patton, Donovan, and Christophers have failed to disclose a single instance of Leishmaniosis in a dog, and they have also failed to transmit the disease to these animals by injection of the parasites into the liver substance and the peritoneal cavity, following the technique which is successful in Nicolle's hands. All of these observers incline to the belief that the Indian form of kala azar is *not* a natural disease of the dog and also that the dog is not susceptible to it. Patton further states that the epidemiological evidence in Madras is not favourable to this theory of dog infection and flea transmission.

Without reflecting in the slightest on the skill and competence of these observers, it appears to the writer that the negative results which they have obtained are insufficient to justify such conclusions. A careful study of the

work which has been done in connexion with the aetiology of the Mediterranean disease, which is being added to almost daily, shows the necessity of widespread search for proof of the existence of spontaneous infection in dogs, and several instances are on record where an exhaustive search of the dog population has been negative in the first instance and positive later. The disease among dogs appears to have its well-defined endemic areas, just as in the case of the human disease, and further, as Nicolle has suggested, seasonal influences may play no inconsiderable part. It may well be, therefore, that further search in other districts, or perhaps even in the same district, may yet disclose the existence of natural infection in Indian dogs. The failure of artificial infection, if confirmed by further experiment, would certainly be a strong proof that we have to deal with two species of *Leishmania*, causative of generalized infection, but the number and duration of those recorded by Indian observers are insufficient to permit of definite conclusions on this point, especially in view of the varying degree of susceptibility which has been shown to be possessed by those animals in, for instance, Tunis and Sicily.

The future will doubtless soon afford a solution of this important question, and the sooner the better, since it is obvious that, until clear evidence of the mode of infection is forthcoming, little can be done in the way of effective prevention.

II.

Infantile Kala Azar. *L. infantum*, Nicolle.

The first cases of this disease were recognized by Pianese and by Cathoire in Italy and by Nicolle in Tunis. In the former country a form of infantile splenic anaemia had long been recognized by Italian physicians, and by some of them its apparently infectious nature had been realized long before the discovery of the parasites. The giant's share in the rapid extension of knowledge as to its association with *Leishmania*, and the mass of experimental and other evidence dealing with the aetiology of the disease, we owe to C. Nicolle and his colleagues at the Pasteur Institute of Tunis, who, during the last four or five years, have issued a long series of valuable reports in the Archives published from their Institute.

The earlier cases were mostly isolated ones detected by Nicolle and his associates in or near Tunis itself but, once attention had been drawn to the fact that this deadly disease existed on the Mediterranean littoral, it was not long before numerous additional districts and countries were signalled as infected. It is impossible at present to assign accurate limits to the Western or Mediterranean form of kala azar, since additional foci are continually being made known, but it is obvious, even now, that practically the whole of the countries bordering the Mediterranean are infected in greater or less degree, and, as was

suggested in the case of the Indian form, it is probable that a mere fraction of the actual number of cases occurring in these countries is at present brought to light.

The known distribution may be roughly indicated as follows: On the southern shore Algeria, Tunis, and Tripoli have all been proved to harbour the disease, while Abyssinia and the Sudan are in parts affected by a kala azar which appears to conform more closely to the Indian type. To the east, Syria is said to be heavily infected. Of the countries bordering or adjoining the northern shore of the Mediterranean we have reports of cases from Crete, the Grecian archipelago, Greece, Turkey, Italy, Malta, Sicily, the Lipari Islands, and finally Portugal. Of these, the island of Sicily and the coast of Calabria appear to be most heavily infected, though it may well be that the greater number of cases reported from these localities is more accurately explained as a measure of the interest and enterprise of the local physicians. However far this distribution may eventually prove to be short of the reality, it will be clear that a form of kala azar is at the present moment widespread in Southern Europe, as well as in Northern Africa, and, since it has been found as far north as Rome itself, there may be reason to dread its extension still farther north, if indeed it does not exist already in Central Europe.

It is not certain whether the infantile type exists elsewhere than round the Mediterranean basin, but Jerusalemy speaks of its presence in China, in the province of Nganwei. Until we have more accurate means of distinguishing the two forms than is afforded by the age incidence and small differences in symptomatology we cannot hope to be certain of this, and it is still far from clear that we have justification for accepting more than one form of the constitutional disease. In India, at all events, cases are met with very frequently in infants and young children, although the disease appears to display a predilection for young adult life; while cases, admittedly rare, have been found in adults in countries affected by the infantile type. For instance, Tashim mentions a case 17 years old at Tripoli, Gabbi one of 18 years at Stromboli, Fulci and Basile a case in a young man of 19 at Rome, and Gabbi another in a man of 38 in Calabria.

However this may eventually be settled, it is undoubted that the enormous majority of the cases occurring in Southern Europe and Northern Africa affect young children of from 2 to 5 years, and in this respect form a striking contrast to the more advanced age incidence of the Asiatic type. The sexes are apparently equally susceptible, and no race appears exempt, to judge from the details of the cases published.

Before dealing with the different branches of the subject *seriatim*, it may be well at this stage to indicate the principal points of difference between the Indian and the infantile forms. Briefly these are the following: (1) The infantile attacks almost exclusively young children, while the Indian is met with at all ages. (2) Certain differences of symptomatology have been described. (3) Cultures of the parasites are readily obtainable upon Novy-McNeal medium in the

case of *L. infantum* and are easily sub-cultured, while, in the case of *L. Dono-vani*, cultures on this medium are as a rule unsuccessful, and sub-cultures cannot be made. On the other hand, cultures of *L. Donovani* succeed in citrated splenic blood and usually fail in the case of *L. infantum*. (4) Inoculation of the spleen parasites into dogs and monkeys reproduces the disease in the case of *L. infantum* and fails in *L. Donovani*. (5) A spontaneous infection of dogs has been found in the endemic areas of infantile kala azar, but no such infection of dogs has been encountered in India.

Morphology of the parasites. A number of careful studies of the morphology of the parasites, as encountered in the body tissues, have been published. Such descriptions correspond extremely closely one with another and confirm earlier impressions as to the great degree of uniformity of structure observable in specimens taken from cases in different districts and countries. All are in close accord with the earlier descriptions of both *L. Donovani* and *L. tropica*. This morphological identity is emphasized by some, for instance by Visentini, and can be confirmed by the writer, who has been unable to detect any constant differential feature between the three species. Forms indicating the mode of growth and multiplication have been closely studied, and division appears to be commenced by amitotic division of the nucleus, which subsequently extends to the cytoplasm. The great number of parasites frequently found in the cells— up to 200—has given rise to discussion as to how large a part is played by phagocytosis. It appears probable that the first parasites are taken into the cell in this manner, but that intracellular multiplication will account for the larger number. Degeneration forms are spoken of by several, and Tomaselli considers that death of the parasite takes place by a vacuolization first of the protoplasm and subsequently of the nucleus, the blepharoplast being the last structure to disappear. In view of the intense vacuolization of the protoplasm exhibited by parasites undergoing rapid development in cultures, the writer is doubtful whether this is to be taken as a sign of degeneration, and whether it may not rather point to an increase in the functional activity of the protoplasm. Forms have been noticed by many observers in which the blepharoplast was absent, and such have been taken to represent a hitherto unrecognized stage of the parasite, degeneration forms, or, as Jemma and di Cristina think, young parasites soon after fission of the mother-cell. The point remains unsettled.

The presence in certain parasites of a third structure in the form of a thread of chromatin substance running from the blepharoplast in the direction of the nucleus, originally noted by Christophers in *L. Donovani*, has since been described by Mesnil and by Novy in *L. infantum*; they consider it to represent a rhizoplast and to stand in an important relationship to the flagellum.

Not infrequently differences in size and shape of the parasites have been mentioned in relationship to the organ from which they were derived ; Pianese, for instance, considered that they were smallest in the liver and largest in the marrow, while those in the spleen were of intermediate size; from this he suggested that the marrow was probably infected first and the liver last. Other

observers, however, do not confirm this difference in size in different organs, at all events as a constant feature in a series of cases.

The blue-staining matrix in which a number of parasites are frequently seen to be embedded is generally accepted as a fragment of the endothelial or other cell in which they were originally contained, but Feletti thinks it may have some nutritive relationship to the parasites which are embedded in it.

Cultures and cultural forms. Artificial cultures of the infantile form were obtained by Nicolle from some of his earliest cases, and he has elaborated cultural methods which have been very successful, both in his own hands and in those of others. Thanks to these methods it has been found possible to make careful investigation of the various stages of the development of the parasites into free-swimming flagellates, and numerous detailed accounts of these forms are now available.

Nicolle first succeeded in his culture of the parasites by employing the medium of Novy and McNeal, which is an agar mixed with defibrinated rabbit's blood; but he was unable to secure any growth in Rogers's medium of citrated splenic blood. The material derived from a splenic puncture was inoculated directly into the condensation fluid at the bottom of a tube of Novy's medium which was kept at a temperature of 20°–22° C. Growth commenced about the seventh day and was abundant by the fifteenth day, numerous masses of parasites in all stages of growth and multiplication being present, the majority flagellated and motile.

Since then Nicolle has simplified Novy's medium by employing only a medium of agar and salt to which is added fresh rabbit's blood, without preliminary defibrination. In this way he dispenses with both peptone and meat extract, neither of which he finds essential. With this modified medium he gets even more rapid and abundant growth and almost invariable success, provided the conditions he lays down are carefully observed. With it he finds growth commencing on the fourth or fifth day and increasing up to the thirtieth day. The formula which is given is the following: agar, 14 grm.; sea salt, 6 grm.; water, 900 c.c., and he lays great stress on the preliminary purification of the agar from impurities and salts by maceration in cold water. This mixture is then sterilized in the autoclave, without previous standardization, and distributed into tubes. The tubes are subsequently melted and then cooled down to between 48° and 52° C., at which temperature one-third of their volume of rabbit's blood is added, taken directly by aseptic puncture of the heart. After the mixture has been allowed to set in an inclined position the tubes are covered so as to protect the contents from evaporation and incubated for two or three days, with the double purpose of proving their sterility and encouraging the formation of condensation fluid. After this the tubes should be kept in the dark, and it is best not to use them for some days. They will keep their nutritive qualities for more than a month. Further details have been given by Manceaux of the points which it is well to observe to get the best results from this modified Novy-McNeal medium, or, as Nicolle calls it, 'N.M.N. medium.'

Another medium has been recommended by Laveran and Pettit as useful when massive cultures are desired for any purpose. The formula of this is:—

Peptone, Chapoteaut	2 grm.	⎫
Sodium chloride	6 „	⎬ 1 vol.
Water	900 „	⎭
Rabbit's blood (defibrinated)		1 vol.

The peptone solution is prepared first and poured into small Roux flasks, an equal volume of rabbit's blood being then added. They have not found any advantage resulting from the substitution of sheep's blood or of market preparations of haemoglobin. The flasks should contain approximately 30 c.c. and should be filled to about one-tenth of their capacity. Incubation is carried out at 21°–22° C.

Rogers's method of employing simply the splenic or hepatic blood, kept liquid by the addition of sodium citrate, appears to have failed in most instances when tried with material containing *L. infantum*; but successful cultivation into flagellate form has been obtained by di Cristina and Cannata, by Longo and by Gabbi. In connexion with this the writer may record that success has by no means invariably followed his employment of Rogers's medium when dealing with cases of kala azar of Indian origin.

In most cases the presence of oxygen appears essential for free growth, but di Cristina and Cannata were only able to get development, of a somewhat weak nature, in citrated rabbit's blood under anaerobic conditions.

In almost all cases of successful cultivation the material has been derived either from the spleen, liver, or bone-marrow of patients or of animals, naturally or experimentally infected, but Novy records a positive result from the inoculation of his medium with the circulating blood of an infected dog. The paucity of the parasites in the circulating blood is against the chance of success in this line, but it is quite possible that, if tried on an extended scale, it might prove a valuable diagnostic method in cases where microscopical examination of the blood failed and splenic or hepatic puncture appeared undesirable.

A great advantage of the methods of Novy and Nicolle lies in the fact that sub-cultures are readily obtainable and that it is possible in this way to maintain in active growth a given strain for an indefinite time. M. Nicolle was good enough to send the writer a culture from Tunis, which reached him, in London, in good condition, and which he was able to carry on through twelve generations, covering a period of over three months, the medium in this case being the original medium of Novy and McNeal.

As to the morphological details of the cultural forms of *L. infantum*, no attempt will be made to summarize the mass of work recently recorded, since this would demand a separate article, and, after all, is not of great practical importance: only a few points will be touched. On the whole it may be said that there is an extremely close relationship between the forms developing from

the parasites of Indian and infantile kala azar respectively; indeed, some who have gone closely into this matter state that they are indistinguishable—for instance, Pulvirenti concludes that they are absolutely identical and believes in the unity of the species. The writer has also made a prolonged study of the two forms, contrasting cultures made by himself and by Statham from Indian cases with cultures of *L. infantum* derived from Nicolle at Tunis. He concluded that small morphological distinctions *do* exist between the two, but has not had the opportunity of determining how far these differences are real and how far they may have been attributable to the different media employed in the two cases. One fact of some importance he was able to elicit, namely, that the parasites of Indian origin *will* grow on Novy-McNeal medium, as in one case he obtained development up to the appearance of flagella; the culture, however, was not vigorous and attempts at sub-culture failed.

Di Cristina and Cannata, as a result of their study of the cultural forms of *L. infantum*, think they obtained evidence of a sexual method of reproduction with the formation of cytogametes and gametes, and further details of these are given by Jemma and di Cristina, but their work lacks confirmation and the subject is too complicated to admit of clear summary.

Parasites with two flagella have been seen by many—the writer has only observed them in the case of *L. infantum*—and their significance is doubtful. In the majority of instances it is almost certainly a case of longitudinal fission of a parasite and early appearance of the second flagellum, but other specimens are not so easily explicable. Jemma and di Cristina think that when seen in stained films they are artifacts, since they have failed to notice them in hanging-drop preparations.

The small fillet-shaped segments, apparently the result of unequal longitudinal fission, which were originally described by the writer from a case of the Indian disease, have been figured and mentioned by several of those who have made a study of the infantile form; they doubt, however, whether the granules which these fillets contain are of true chromatin nature, and their significance is still uncertain.

The importance of the study of these flagellated cultural forms is not only considerable on phylogenetic grounds and for the determination of the number of species of *Leishmania*, but has, obviously, an intimate bearing on the etiology of the different diseases caused by this genus. Although test-tube experiments have their obvious limitations—somewhat unduly emphasized, in the opinion of the writer—there can be little doubt that the forms encountered in these artificial cultures are the forms which will be found in the transmitting ecto-parasites and which already appear, as will be seen, to have been found in the case of the infantile form of kala azar. In this connexion the almost universal failure in infantile kala azar to infect by means of cultures—Novy alone has succeeded in infecting dogs with a massive dose—suggests that, before successful infection can take place, it may be necessary for the flagellate parasites to assume a post-flagellate form, to follow Patton's nomenclature, and that only

in this form can they effect a lodgement in the tissues of their new host. Some support of this view may be found in the fact that the fate of flagellates inoculated into the body is to be speedily phagocyted and destroyed; this has been noticed in mice by Delanoe, and the writer can add that he has observed intense phagocytosis of the cultural forms of *L. infantum*, *in vitro*, when placed in contact with his own leucocytes at a temperature of 37° C. In this case there was no doubt of the destructive action of the cell juices, as the parasites, even when fully formed, motile and flagellated, were rapidly disintegrated, and in a very short time nothing was left but a little granular débris lying in the vacuoles formed in the polynuclears during the process of digestion.

Animal experiments. The parasite of infantile kala azar has proved to be capable of infecting animals, and in this respect presents a striking contrast to the Indian form, with which, as has been said, no positive results have so far been obtained. The animals which have shown themselves most susceptible are the dog and the monkey, though slight infections have also been recorded in mice, white rats, guinea-pigs, and rabbits. In addition, the very important observation has been made of spontaneous infection in dogs. This spontaneous canine kala azar will be considered separately after the experimental forms of animal infection have been dealt with.

Experimental infection of dogs. Nicolle, as has so often to be recorded, was the first to succeed in this by inoculating some emulsion of spleen tissue, rich in parasites and derived from one of the earlier child cases, directly into the liver substance of a dog and also into its peritoneal cavity. The dog showed no symptoms and, $2\frac{1}{2}$ months later, was given a similar dose from another case. The animal was sacrificed on the 159th day after the first inoculation, and parasites were found in the spleen and, more rarely, in the liver. This experiment has been repeated by Nicolle and his co-workers on numerous occasions, and has also been confirmed by many other workers, the virus being derived either from a human case or from a dog previously infected. A study of these cases, however, makes it clear that the almost invariable success which attended Nicolle's experiments—he mentions one series of eighteen positive results among nineteen dogs—is not attainable in all instances; for example, Jemma and di Cristina found many dogs refractory even to massive doses of the virus It appears extremely probable that differences as regards susceptibility exist in different breeds of dogs, if indeed some breeds are not altogether refractory. As has been pointed out, such differences in susceptibility may in part be accountable for the failure to infect dogs in India.

With the single exception of Novy's experiments, mentioned below, the material used for inoculation has invariably been an emulsion of spleen, liver, marrow, or other organ containing the intracellular forms of *L. infantum*; inoculation of cultures from which these forms are absent has failed. In most instances the original technique of Nicolle has been followed in the mode of inoculation, namely, the simultaneous inoculation of this emulsion into the liver substance and into the peritoneal cavity. Infection has, however, frequently

followed inoculation into one or other site alone, and those who have experience of both methods think the peritoneal channel is preferable and more certain. Numerous attempts at infection by means of intravenous inoculation have failed. Subcutaneous inoculations have also given negative results, at all events as regards the induction of a generalized infection, but Nicolle and others have at times noted a local reaction at the site of inoculation, from which parasites were recovered, which is of interest in connexion with the aetiology of tropical sore ; the histological characters, however, of these rare local lesions in no way resembled those caused by *L. tropica*.

The symptoms of experimental infection in the dog correspond closely with those of the spontaneous infection in these animals. The disease may assume one of two forms, an acute form which is often fatal in three to five months and usually occurs in young animals, or a mild form which is very chronic and occurs more often in older dogs. The acute form is accompanied by irregular fever, progressive wasting, motor disturbances involving the hind-legs, occasional diarrhoea, and the animal dies in a comatose condition. In the chronic form, on the other hand, although some of the above symptoms may be present, the animal may show practically no signs of disease and may remain in apparent good health, except for some loss of weight. The existence of the latter type of infection naturally adds to the difficulty of determining whether infection has resulted from the inoculation, and emphasizes the importance of satisfactory methods for diagnosing the disease in dogs. Symptoms being obviously unreliable, recourse must be had to the demonstration of the presence of the parasites in the body. The parasites are almost always present in the spleen, liver, and bone-marrow of infected animals and, though rarely, may also be found in the peripheral blood, especially at such times as high fever exists. The infrequency of their presence in the blood necessitates search being made in one of the other infected organs or tissues. Spleen puncture in the case of a dog is impracticable in view of the impossibility of locating this organ with accuracy. Liver puncture is easy, and is the method usually employed, but it has the disadvantage that parasites may not be found, although a subsequent post-mortem examination may reveal their presence in abundance in the organ. Examination of a sample of bone-marrow is coming to be more frequently relied upon, a small sample being obtained by trepanning the femur or the tibia ; in the hands of Italian workers this method has given good results, and it appears of especial value in experiments conducted in areas where the spontaneous disease exists or is suspected, since it is possible in this way to ascertain with a fair amount of confidence that dogs which are intended to act as controls or to serve for infection experiments are normal and free from all traces of infection.

It is possible that cultural methods applied to the blood or to material derived from some organ or tissue may give a positive result even when careful microscopical examination has been negative. Laveran and Pettit, for instance, mention a case in which splenectomy was performed and cultures made from the organ were positive in spite of the failure to detect the parasites in stained films.

The very chronic nature which the experimental form may assume is illustrated by two cases recorded at Tunis in which the animals died after seventeen and eighteen months respectively, without having shown any marked symptoms ; in one of these cases the infection of the organs was found to have been intense. There does not appear to be any relationship between the size of the infecting dose and the subsequent attack ; a very small number of parasites may give rise to an intense and fatal attack and a massive dose to a mild one, or it may even fail, and this when working with the same virus.

Experimental infection of monkeys. These animals were proved to be susceptible by Nicolle shortly after he had succeeded with dogs, and the method of infection and the character of the attack follow much the same lines in each. On the whole, the symptoms are more manifest, and of seven *Macacus sinensis* inoculated by Nicolle two died within three months. The well-known delicacy of these animals in captivity, even under the best conditions, makes it, however, difficult to judge points such as this. A case was noted in which the animal showed no signs at all during life, but was found after death to be heavily infected. A point of some interest is that in several cases parasites have been detected in the hepatic cells, an extremely rare condition in man, if it ever occurs, and one which Nicolle has only met with once in the dog. Later experiments were carried out with another species of monkey, *Macacus cynomolgus*, which proved to be equally susceptible to *M. sinensis*, and possibly a little more so since in one animal a petechial eruption was noticed in the course of the disease, and this had not been encountered in *M. sinensis*.

Infection of the smaller experimental animals has in most instances failed, but Laveran and Pettit, by inoculating material derived from an infected dog, noticed a slight infection in the case of the mouse, the white rat, and the guinea-pig, parasites being found in mononuclear cells of the peritoneal exudate as late as fifty-nine days after the inoculation. Volpino, too, has recently succeeded in producing a keratitis in the cornea of the rabbit by the inoculation of parasites into the scarified surface of this tissue ; three months later the portion of cornea examined was found to contain *L. infantum* in large numbers.

A few other points may be noted in connexion with these very numerous animal experiments. In a few instances opportunity was afforded of examining foetuses of infected dogs ; in no case were they found to be infected ; we have, therefore, no suggestion of the possible hereditary transmission of the disease in dogs. Splenectomy has been performed during the course of the infection in dogs and monkeys without in any way modifying the progress of the disease. Passage of the virus from dog to dog is readily procurable, and may apparently be carried on indefinitely ; no marked alteration in the virulence of the strain is apparent. On the other hand, passage of the virus through monkeys has been found by Nicolle and Manceaux to result in the diminution of the virulence for the monkey, but not for the dog.

Infection by means of cultures. The whole of the experimental work dealt with above was the result of infection with the non-flagellated parasite, as it is met

with in the tissues of man and infected animals. Numerous attempts to produce infection by means of the flagellated forms which develop in artificial cultures have been made in Tunis, Sicily, Italy, and elsewhere with universal failure except in the hands of Novy. He thought that the failures might possibly be due to the employment of too small doses, and in consequence gave repeated and large doses to a dog and succeeded in infecting it. The strain with which he worked was derived from Tunis, and had been sub-cultivated through so many generations that it was hardly possible that any of the pre-flagellate forms could have persisted in a living but undeveloped state. In all he gave fifteen inoculations to the animal, spread over a period of $4\frac{1}{2}$ months, the doses varying from the contents of 8–40 culture-tubes : the total amount corresponded to the growth from 270 culture-tubes of his medium ! The animal remained in good health in spite of this colossal dosage, but when killed was found to be infected, the parasites being numerous in the cells of the spleen and liver, but mostly free. Cultures made from the infected organs were also positive, proving the vitality of the organisms.

Repeating this experiment, he records in a later publication the infection of five other dogs, and that he was able to secure infection by a single inoculation of the material from 20 culture-tubes. He recommends for diagnosis during life cultivation of the blood, 10 c.c. being collected and distributed over 20 tubes of culture medium.

These observations of Novy's are naturally of great importance, and, as he points out, establish the susceptibility of the dog to cultural infection and complete the chain of evidence regarding the relationship of the parasite to the disease.

Spontaneous infection in dogs. Here, too, we are indebted to Nicolle for the recognition of the important fact that parasites indistinguishable from *L. infantum* occur in dogs and cause in them a disease presenting a resemblance in many ways to the infantile form of kala azar. On finding that dogs were susceptible to the disease on inoculation of the infantile virus, he searched first for evidence of any association between actual cases in children and dogs, and in several instances such information was forthcoming, children who had contracted the disease being found to have lived in intimate association with dogs, some of which died during this time, or subsequently, of an indefinite disease. Next, he made a systematic examination of the dogs which were destroyed at the *fourrière* in Tunis, and soon found one which harboured the parasites in its organs.

Since then large numbers of dogs have been examined and other cases found. In his first series 4 infected animals were found in 220 examined, while in a more recent series carried out at Tunis by the Yakimoffs 5 were found infected out of 299, a percentage of 1·67.

Search for the existence of this spontaneous infection of dogs was soon instituted in other districts in which infantile kala azar had been found, with the result that, almost without exception, infected animals were detected. In

two instances parasites were found in dogs in localities in which infantile kala azar had not been recorded, but each of these announcements was speedily followed by the discovery of cases whose undoubtedly genuine character was demonstrated by the finding of the parasites on spleen puncture. These were, first, Algiers, where Edmond and Étienne Sergent first found 9 dogs infected out of 125 examined, a percentage of 7·2, and where Lemaire subsequently found a human case. The second instance was at Rome, in which the presence of the infection in dogs was first recorded by Basile, and not till later was the first human case reported by Fulci and Basile. At the present moment it may be said that in every country in which search has been made and in which infantile kala azar has been proved to exist, spontaneous *Leishmania* infection of dogs has also been found. The only exception so far reported is at Palmero, where infantile cases occur, but in which Jemma and di Cristina examined 300 dogs with a negative result.

The percentage of infected dogs in a given area seems to vary considerably. In an endemic focus of the disease discovered at the village of Bordonaro in Sicily by Gabbi, an investigation of the dogs by Basile showed the heavy infection of 27 out of 33 dogs examined. At Rome, just referred to, Basile found also 16 infected dogs out of 60 examined, but by reason of the diagnostic methods employed was inclined to believe that this was an underestimate of the degree of infection. Alvares and da Silva found 1 infected dog out of 19 in Lisbon, where the infantile disease exists. Nineteen infected dogs were found among 284 examined by Cardamitis in Greece, of which 15 out of 184 were in the city of Athens itself. Critien at Malta found 3 infected out of 30 examined, and in this instance also the human infection is known to co-exist with the canine.

Negative results were obtained by Fülleborn with 50 dogs in Hamburg, where there is no suspicion of the human disease, and Donovan's negative results at Madras may also be recalled, though connected with the Indian form, as he has examined 1,150 dogs there without finding any trace of *Leishmania*. Finally, Bousfield found parasites in a dog in the Egyptian Sudan which had been in association with one of the human cases of the kala azar which is met with there, although it remains doubtful to which group these Sudanese cases are to be joined.

Pathological anatomy. There is a very close correspondence, if not absolute identity, between the infantile and the Indian forms as regards the distribution of the parasites in the body and the histological changes which their presence causes. As regards distribution, whatever blanks may be noted in connexion with one series of cases could be filled in from the results of another investigator. The sites in which the parasites are most abundant, and in which they seem almost invariably to occur, are the spleen, liver, and bone-marrow; but besides these, they have also been found in the kidney, the lung, the pancreas, the mesenteric and other groups of lymphatic glands. Critien has also recorded finding them in mucous flakes passed in the stools of a three-year-old child at Malta, the first observation of this kind in either form of the disease.

The histological changes induced in these tissues have been the subject of much careful study by Pianese, Jemma and di Cristina, and others, and their results are in the closest agreement with similar studies made on the Indian disease. The irregular distribution of the parasites in a given organ has been remarked on many occasions, and the histological changes in such organs are, as one would expect, largely dependent upon the degree of cellular infection.

The changes in the spleen have been closely investigated, especially by Italian workers, and Pianese considers that the essential features are a well-developed fibro-adenitis, the elastic tissue remaining normal; the cells of the follicles become involuted and assume an epithelioid character; there is also a diminution of the spleen pulp in the areas where the 'macrophages' are abundant and the venous spaces appear to be dilated.

Nothing differing from the Indian form has been noted as to the distribution of the parasites and the histological alterations in other situations. From a study of the experimental disease it appears probable that the endothelial cells of the lymphatics and smaller capillaries of the organ concerned are first invaded.

The comparative rarity of bowel symptoms of a dysenteric character in the infantile form is notable, and this is reflected in the rarity with which intestinal lesions have been mentioned; at the same time, Jemma and di Cristina found the parasites in the follicles of the large intestine in one of their cases, and the observation of Critien has already been mentioned.

Treatment. Up to the present, the treatment of infantile kala azar stands in no better position than that of the Indian disease, although the former now possesses the great advantage that dogs and monkeys can be infected, and it is therefore possible to carry out on these animals tests of various particular therapeutic measures. Experimentally infected animals have been largely used for this purpose, but, although certain drugs give encouraging results with such animals, nothing but persistent failure seems to follow their application to the sick child. There is, however, no reason to despair of ultimate success, and encouragement may be drawn from the fact that cases of spontaneous cure in children do occur, while it is also possible that the apparent limitation of this form to young children may be partially due to adult immunity, acquired by unrecognized attacks in childhood.

A long list might be given of the drugs which have been tried in recent years, but only a few will be mentioned. No one has a good word to say for quinine, whose failure has indeed come to be looked on as one of the symptoms. Atoxyl has been tested exhaustively, on many systems of dosage and inter-spacing of individual injections, but although some cases appeared to improve there is no record of recovery attributable to its action. Domela, however, appears to have a higher opinion of its value, though the case he recorded could not be claimed as a cure at the time he wrote. Arsenophenylglycin was employed in a fair number of cases but has not been of any benefit, and the experiments which Nicolle and Comte carried out with it in dogs experimentally infected were not encouraging; indeed, the disease appeared more severe in the case of the treated dog than in the untreated control.

Electromercurol has been employed by Nicolle and by Cortesi and Lévy, by intramuscular injection, and has been pushed as regards dosage to its limits, but with the usual result of failure. Colloidal electrargol and colloidal thiarsol also failed to do any good when tried by Cortesi. Jemma, however, speaks of the value of Röntgen rays and believes that the disease is curable. Morpurgo employed small doses of arseniate of soda, but without effect.

The striking results which have attended the employment of Ehrlich's new remedy '606', or dioxydiamidoarsenobenzol, in syphilis and other spirilloses has led to its being tried in many other affections, and hopes were entertained that it might be beneficial in kala azar. There are now on record a fair number of cases in which it has been tried, but so far with no better results than have followed other arsenical preparations. At the same time there remains some hope that further experience may prove more satisfactory, since experiments on dogs have apparently shown that this drug, alone of all that have been tried, is capable of killing the parasites, at all events in some instances. In the first of these experiments Nicolle and Conor inoculated 20 cg. into the thigh muscles of a dog of 11 kilos which had been infected by intraperitoneal inoculation, and in which two successive punctures of the liver had shown the parasites to be increasing. Four days later, puncture of the liver in three places failed to disclose any parasites, and a subsequent trepanning of the tibia yielded a similar negative result. The animal, which remained in good health, was killed on the thirty-fifth day and no parasites could be found in any organ. This result naturally gave rise to great hopes that arsenobenzol might abort the human affection in similar manner, and at Tunis and elsewhere it has been tried on children, but there is no case of recovery up to the present moment. It appears to be in the main a question of dosage. In the case of the dog the sterilizing dose seems to approximate 2 cg. per kilo of body weight, and such a dose would be dangerously near the toxic dose for a human being. Nicolle also points out in this connexion that the experimental disease in the dog is comparatively mild and frequently terminates in spontaneous recovery, while in the child the tendency is towards a fatal issue, and that this fact, in addition to the greater tolerance of the drug by the dog, may explain the contradictory results so far attained. At the same time he thinks that further experience may be more successful, and he intends to administer the arsenobenzol in his next cases by the intravenous method; hitherto it has always been given intramuscularly and in doses which could not be expected to be of much service. Further encouragement is to be derived from the good results reported of the action of '606' in tropical sore by Manceaux, and the results of its further trial in infantile kala azar will be awaited with great interest.

Fresh bone-marrow, the use of which was advocated some years ago in the Indian disease, has been tried by Sluka and Zarfl, but appeared useless; and hectine, which was used by both Mara and Conseil, does not appear to be any more reliable, although the case treated by the latter gave some signs of improvement.

Aetiology. Progress in the elucidation of the mode of infection in infantile kala azar has been remarkable during the last two years; fact has been added to fact, and the whole now pieces together in a most convincing manner. It may still be too early to speak of the aetiology as completely clear, but the observations summarized below will show how little doubt can remain that canine kala azar is identical with infantile kala azar and that the transmitting agent is a flea, either the dog-flea, *Pulex serraticeps,* or the human flea, *Pulex irritans.*

As soon as Nicolle had found that the disease could be transmitted to dogs and had further discovered the existence of the spontaneous infection in these animals, he naturally sought for evidence of any connexion between infected children and dogs. This was speedily forthcoming, as two of the first four cases were known to have lived in close contact with dogs, while in one instance the dog in question had been ill and had died. He suggested, then, the natural hypothesis that some ecto-parasite of the dog might prove to be the transmitting agent between dog and child. It soon became manifest that this association between dogs and infected children was of frequent occurrence and, further, that localities where infantile kala azar was found were also localities in which the spontaneous disease in dogs occurred in endemic form.

It is true that cases in children were found in which no close association with dogs could be proved, and others in which the dogs of the house were examined and found to be in good health; such observations, however, are not surprising in view of what has been said as to the difficulty of diagnosing the affection in dogs and the existence of the chronic and mild form in which the dog shows few if any signs of illness.

Cases were soon on record in which infected animals were found in houses in which the human disease was present or had been present, and this was shortly followed by the discovery of what appeared to be *Leishmania* parasites in fleas taken from infected dogs, as was done both by Basile and by Sangiorgi, the material in each case being derived from Sicily. The demonstration of the pre-flagellate forms of *Leishmania* in the gut of fleas collected from an infected dog, though interesting and suggestive, was more or less to be expected, as we already know that at times a fair number of parasites may be found in the circulating blood of the dog, but it was further noted that the parasites appeared to undergo development in the flea, similar to that which takes place in the culture-tube. This latter fact added to the probability that the flea was a true intermediate host. Further search was made in fleas collected in endemic areas of the human disease, not from infected dogs, but from the coverlets, pillows, and mattresses of houses in the affected areas, and protozoal organisms resembling the cultural forms of *Leishmania* were found in a certain small percentage of these. Sangiorgi, for instance, found such organisms in 14 out of 378 dog-fleas collected in Catania, and Basile had a similar result with fleas collected from mattresses, &c. in Bordonaro, the village in which both the human and the canine affections are so frequent. Further confirmation came from Lisbon, where Alvares and Da Silva found all stages of *Leishmania* in a flea taken from

an infected dog; they also examined sixty fleas collected on healthy dogs with negative results.

The notorious difficulties connected with the proof of insect transmission of flagellated protozoal organisms were to be anticipated here, for, however close the resemblance of such forms as are found in the digestive tubes of the insect to the cultural forms already known, it is hard to distinguish them from other flagellates which may be common parasites of the particular insect in question. Flagellate parasites have been described in fleas by Balfour, by Patton and by Mackinnon, and if the observations had stopped here there would have remained abundant material for scepticism as to the genuine character of the flea as a true host, but fortunately further proof of an experimental nature has recently been obtained, principally from the work of Basile.

Basile's first experiment, aiming at proof of the infectivity of a flea which harboured *Leishmania* parasites, was conducted in the following way. Fleas were collected from a dog which had been proved free from the disease; these were placed in vessels containing some spleen pulp taken from an infected dog and rich in parasites, and on this some of the fleas fed. After a time, the fleas were killed and dissected. One portion of the gut contents on being searched and showing the presence of the parasites, the other portion was emulsified and injected into a young puppy, whose marrow had previously been examined with negative results. The puppy was infected and *Leishmania* parasites were subsequently found in its peripheral blood. It was further noted that the parasites found in the intestine of the flea were far more numerous than in the spleen pulp on which it had fed, and numerous division forms were seen. The fleas employed in this experiment were *Ctenocephalus* (*Pulex*) *serraticeps*.

A later experiment, and one more closely imitating what might be assumed to occur in nature, was next carried out. Two pups, which had been born in the laboratory, when thirty days old were placed in a special cage, which had been thoroughly disinfected, after having been proved to be free from kala azar by examination of the bone-marrow. The cage was protected by netting fine enough to ensure that no fleas or other parasites could gain entrance from outside, and the temperature was maintained at about 20° C. as the experiment took place in the winter. After a few days a dog infected with the disease was placed in the same cage, so that there was no obstacle to its numerous fleas passing to the uninfected pups. Thirty days later, liver puncture of the two pups showed that each was infected, *Leishmania* parasites being found on microscopic investigation. Control pups, from the same litter, remained in good health and showed no infection.

At a later date this experiment was repeated by Basile under somewhat different conditions. Again he employed young pups which had been born in his laboratory, and he took the same precautions to ensure that they were uninfected. When they were about a month old four of the litter were placed in a disinfected and gauze-protected cage, the two remaining pups being kept as controls. The cages were so situated that no contact with other dogs was

possible. In this instance infection was introduced among the dogs, not in the person of an infected animal, but in the shape of fleas which had been collected at Bordonaro, an endemic focus of the disease, from coverlets or mattresses in houses where dogs were kept. Repeated examination of the blood of the dogs and hepatic punctures gave negative results until about two months after the fleas had been admitted to the cage, when two of the dogs were found to be infected. All of them had for some time shown irregular temperatures and were getting thin. Within six days of the demonstration of the parasites in the first two dogs the whole four died, and on examination all were found infected with *Leishmania*. The two control dogs, which had remained in good health, when sacrificed later were found to be completely free from the disease.

Basile concludes from the result of these experiments and the rigorous conditions under which they were carried out that they prove beyond dispute the fact of flea transmission.

Further communications, published in July of this year, gave further evidence in support of the above conclusion and again demonstrated that dogs could be infected at a distance by the bites of fleas collected in a house in which was a case of kala azar. In addition, the important observation was made that not only *Pulex serraticeps* but also *Pulex irritans* were found to contain parasites indistinguishable from the cultural forms of *Leishmania infantum*. Pianese's latest communication, in collaboration with La Calva and Visentino, gives further evidence that both *serraticeps* and *irritans* are concerned in the spread of the disease, and they conclude that the human and canine Leishmaniosis of the Mediterranean are identical, and that these two fleas are the intermediate hosts and the transmitting agents from dog to man, from man to man, from man to dog, and from dog to dog.

Confirmation of part of Basile's work is already forthcoming, since Alvares and Da Silva have found in three fleas taken from an infected dog in Lisbon every stage of *Leishmania*, including fully flagellated forms and typical rosettes ; the writer has had the opportunity of examining the excellent microphotographs which they have taken from the gut contents of these fleas and is quite in agreement with the authors that they are indistinguishable from the cultural forms usually seen. In addition to this they made the interesting observation that the parasites are passed in the faeces of the flea ; this they ascertained by confining the fleas in a vessel with a glass plate at the bottom on which the fleas voided their excrement ; this being subsequently stained and examined proved to contain all the forms seen in the gut, including rosettes. They conclude from this that the mechanism of infection may be similar to that which occurs in the transmission of plague through the bites of *Pulex cheopis*, where, as shown by the Indian Plague Commission, it is probable the faeces passed while the insect is feeding are rubbed into the bite together with the plague bacteria which they contain.

Whether fleas are the only intermediate hosts remains to be proved ; there is nothing improbable in the conjecture that ticks, lice, bugs, or biting insects may

at times act in a similar manner, but, at the present moment, there is nothing but the slightest evidence tending to incriminate any of them.

III.

Tropical Sore. *L. tropica*, Wright.

Since the first observation of the presence of *Leishmania* parasites in a tropical sore by Wright, in 1903, a great number of accounts have appeared, confirming their presence in the tropical sores peculiar to particular countries or districts. Up to that time there had been considerable doubt as to the identity of the various sores common in many parts of the tropics, and this doubt is reflected in the innumerable synonyms by which the lesions are known. One after another these lesions were searched for the new parasites, and, practically without exception, they were readily detected. Without attempting to give a complete list of the various names, the following may be mentioned : Aleppo boil, Armenian boil, Persian boil, Delhi boil, Frontier sore, Bagdad sore, Biskra boil, Gafsa boil, Nile sore, and innumerable others. The more general terms of Tropical sore, Oriental sore, and *bouton d'Orient* have also been freely employed by those who believed in their identity on clinical grounds. Of these general terms, the two latter are no longer appropriate, since the affection is now known to exist in the New World as well as in the Old, and even the term tropical sore, adopted in the present instance, is no longer strictly accurate, since their presence on the northern shores of the Mediterranean has been recognized.

Besides confirming the identity of the sores so long familiar to tropical physicians in many parts of the world, the easy demonstration of the parasites has led to the detection of tropical sores in countries hitherto unsuspected. Of these, the following may be mentioned : *Asia*, Bettman and Wasielewski describe a case from Central Asia and Nicolas thinks it is common in New Caledonia ; Marzinowsky also reports more cases from Transcaucasia in addition to those in which he first identified the parasites, independently of Wright. In *Europe* chief interest attaches to the discovery of the existence of this form of Leishmaniosis on the Calabrian coast of Italy by Gabbi and Lacava, while Cardamitis and Melissidis have also found it in Crete and Reinhardt in Constantinople. In *Africa* new foci have been demonstrated in Algiers and other parts of the northern coast and at Zinder in Northern Nigeria, where Stevenel has shown it to be identical with the disease known locally as ' Cro-Cro '. Benoit-Gonin also speaks of it as common on the upper reaches of the Niger itself. *America*, too, has been shown to be no longer exempt, as had been believed for so long, and apparently cases are far from uncommon in several parts of Brazil and on the Amazon, as has been pointed out by Paranhos and Marques, Carini, Lindenberg and others. In this country the local name of ' Bauru ulcer ' appears to have been used for some time and the majority of the cases have been found in the province of São Paulo. Trinidad and the Canal

Zone of Panama have been found by Darling and Connor to harbour the disease, and there can be little doubt that further extensions will soon be made to the geographical limits of the American form. It has been suggested that the disease may have only recently been imported into Central and Southern America, and Carini and Paranhos mention that their first case was that of a Syrian who had recently come from Beirut, but at the same time they add that a similar type of sore has been known in Brazil at least since 1895.

Morphology of the parasites. If differences exist between *L. tropica* and the other species they must be very slight, since the great majority of observers who have had the opportunity of comparing them are agreed that they are morphologically indistinguishable. The description of one holds good for the others. The few special points which may be noted are that Nattan-Larrier and Bussière have sometimes seen a delicate filament connecting the blepharoplast and the nucleus which they do not think corresponds to the rhizoplast described by Novy in *L. infantum* and by Christophers in *L. Donovani.* Several observers have studied the fresh parasites and all are agreed that they show no motility. In most instances the parasites are intracellular and only rare free forms are to be seen, but Cardamitis, in his study of the Cretan cases, found the reverse, namely, that they were almost all free and isolated and only a few intracellular; it may be noted that the sores he examined were not ulcerated. The size of the parasites in comparison with that of the other species has been the subject of some difference of opinion, some holding that they are larger on the average than those of the constitutional disease, and others that they are smaller. The point is not one of value in differential diagnosis, since it is abundantly clear that there are wide variations in this respect, even in a single species, and that the size and shape may be influenced by the site and probably also by the rapidity of growth and the stage of development. As far as the experience of the writer goes he has found the parasites somewhat larger in tropical sore than in the other species, but he is not inclined to lay any stress on this.

Forms which apparently indicate a multiple division of the parasites have been described by Lindenberg and others, but Marzinowsky, from his observation of living specimens, does not agree with this and considers they are due to compression within the cells, since he has noted such forms on escaping from the cell to resume their usual shape and appearance.

Cultures and cultural forms. Artificial cultures of *L. tropica* are as readily secured as those of *L. infantum,* but, apparently, both of them are much more sure of success than in the case of *L. Donovani.* As to the medium employed, there does not appear to exist here the distinction between *L. Donovani* and *L. infantum,* since it has been found possible to secure good flagellate development of *L. tropica* in citrated human blood, as has been done both by Row and by Marzinowsky, and also in Novy's medium, as recorded by Nicolle and his colleagues and also by Marzinowsky.

Considerable differences, however, are to be noticed in the temperatures which have been observed for cultivation. While Nicolle and others cultivate at

22° C., Row reports good development between 25° and 28° C. and Marzinowsky's cultures were maintained at 37° C. This difference is certainly noteworthy, since little evidence of growth can be obtained in the case of the two kala azar parasites above 25° C. At the same time, it is only at the lower temperature that successful sub-cultures can be secured and a strain kept going through many generations. Nicolle, for instance, mentions a culture, of human origin, of the thirty-third generation, while Marzinowsky, working at 37° C., was only once successful in obtaining a sub-culture.

In the cultural forms, as in the intracellular forms, no distinction can be observed between the three species. Nicolle in his earlier work was inclined to think that small differences, which he described in detail, did exist, but in a later communication he states that the cultural forms of *L. tropica* are absolutely identical with those of *L. infantum*. At the same time, Nicolle and Manceaux have noted that at the end of the optimum period of growth, eight to ten days, cultures of *L. tropica* are always more abundant than cultures of *L. infantum*.

Marzinowsky's studies of these cultural forms have, however, led him to conclusions widely differing from those of other observers. He believes that they afford evidence of a sexual process, and he describes as male forms comparatively small parasites with a large nucleus and pale-staining protoplasm, and as females larger parasites with a small nucleus and a protoplasm which stains deep blue. As development advances he says these distinctions, with the exception of the difference in size, are lost. He also thinks that he has observed a process of conjugation between a male and a female parasite in which the two merged into one and their nuclei became fragmented, the particles being distributed throughout the common mass of protoplasm. After this fusion he says that the flagellum disappears, the parasite lengthens out and becomes motionless, and the blepharoplast also vanishes, while a single large nucleus makes its appearance and is situated centrally. This he thinks is the end of the cycle, as observable in cultures, though it probably is continued in the body of the intermediate host, whatever that may prove to be. These views will of course need full confirmation, and all that need be said at present is that the temperature at which these experiments took place was far in excess of that used by any other worker and may have had a bearing upon the appearances which he has described.

Animal experiments. The virus of tropical sore, like that of infantile kala azar, has been successfully inoculated into both monkeys and dogs with the production of local lesions, closely resembling those which are found in man, in which the parasites are found in the cells and from which they may be cultivated. Nicolle and Manceaux have succeeded in infecting these animals not only with material derived directly from a human source, but also by means of the inoculation of the flagellated cultural forms, the lesions produced by these two methods being identical. They found, however, that it was impossible to produce any pathogenic effect by the intravenous inoculation of cultures which were infective when rubbed into the skin. In the case of the monkey the site they

found best was either the eyebrow or the skin at the root of the nose, and in this animal the duration of the lesion was only twenty-one days. The incubation period in the dog was about a month, and they were able to prove that one attack of the sore in this animal as a rule gave complete immunity against a subsequent inoculation of the virus; on the other hand, the intraperitoneal inoculation of even 100 cultures of the parasite failed to produce any disease or to give any immunity to those animals.

Row, working in India with material from human sores in Cambay, was also successful in infecting *Macacus sinensis* by rubbing the human material directly into a scarified surface, but he was not successful with the inoculation of cultures. He finds some differences in his monkey results as compared with those of Nicolle and Manceaux, in such points as the incubation period, the number of parasites in the lesion, the characters of the lesion, and in the fact that he found the animals susceptible to another infection during the progress of the first lesion. None of these differences, however, appear of great importance, and it is probable that extended experience will attribute them to differences in the susceptibility of the experimental animals or other variants.

A few of the other facts determined by animal experiments with *L. tropica* will be referred to later in connexion with the question of immunity.

Pathological anatomy. The histological characters of tropical sores and the distribution of the parasites therein has been the subject of elaborate studies by a number of observers, but no analysis of this side of the affection could be undertaken without unduly prolonging this article, and it appears the less necessary since the work of Bettmann and von Wasielewski, of Nattan-Larrier and Bussière, and numerous others, is available to those who would wish to go further into the subject. No more will therefore be attempted than reference to a few of the points recently brought to light, especially to such as have any relation to the problem of aetiology.

In almost all instances the parasites are found inside cells and only a few of them free, but since the studies on which such observations are based were mostly sections of tissue, it must be very hard to be certain as to whether a particular parasite is really extracellular or has merely been pushed out of position by the action of the knife. The nature and origin of the cells which harbour the parasites occupy a large portion of the contributions dealing with the histology of tropical sore, and all are agreed that most are mononuclear cells, though wide differences of opinion are held as to their nature and origin. Giant cells have been noticed in many cases, and in some material sent from Guiana parasites have been found in such cells by Nattan-Larrier, Touin, and Heckenroth. No mention of the occurrence of parasites in plasma cells has been made. As to their presence in leucocytes, a point of obvious importance in connexion with aetiology, they are commonly seen in what are called large mononuclear leucocytes, and have also been found by several observers in polynuclear leucocytes. The latter site at once suggests the possibility of the parasites being carried by such cells into the circulating blood, but, although very careful search has been

made for them in the peripheral blood, there is at present only one observation of their being found, Neumann recording their presence in blood drawn from the finger in a patient who had a tropical sore on the forearm of the same side.

The distribution of the parasites in the lesion differs according to the stage of the sore, and the common experience is to find them in greatest number in the cells at the margin of the lesion and in its depths, when the boil is young and especially before it has ulcerated. In contrast to this, however, Marzinowsky states that he found them most numerous in older lesions, and especially in those which showed a tendency to cicatrization.

The gross characters of the lesions have been often described, but, now that the presence of the parasites gives certainty of diagnosis, the differences which are being recorded assume a greater importance, and there is an obvious tendency nowadays to believe that it will be necessary to subdivide these cutaneous forms of Leishmaniosis. The non-ulcerating form described by Thomson and Balfour in the Sudan may perhaps be taken as the type of one of these future subdivisions, and there is much in support of the views of those who think that the American cases will also prove to be due to a different species. At the present moment, however, there is no evidence strong enough to admit of any such subdivision of *L. tropicum* into sub-species or new species.

Another point of interest is that the sores may sometimes be found on mucous membranes as well as on the skin; this has been recorded by Cardamitis and Melissidis in a case which suffered from no less than thirty-five boils on the face and arm and in which the mucous membrane of the lip was also involved, while Carini, in connexion with the American form, says such cases are not uncommon and that ulcerations of the palate and the buccal and nasal mucous membranes, in which *Leishmania* can be demonstrated, are graver in their nature than similar lesions of the skin.

Aetiology. Recent knowledge, although full of facts which are suggestive, has afforded no definite explanation of the aetiology of tropical sore. In this instance we know neither the alternative host, if one exists, nor the transmitting agent, which almost certainly must exist. The developments in connexion with infantile kala azar and its apparent mode of infection naturally direct attention to the dog and the dog-flea, especially since the two diseases are found side by side in many places, but, in spite of the fact that it has been found possible to transmit the disease to the dog by the inoculation, there is no evidence of the existence of tropical sore as a spontaneous infection of these animals. The only exception is a very doubtful one. A large number of sores were found on an emaciated and moribund dog by Dschunkowsky and Luhs, and after death they found the organs heavily infected with *Leishmania*. Although some parasites were found in the sores it may only have been a case of canine kala azar.

The well-known fact that the sores are almost always on exposed parts of the body has influenced the many theories which have been advanced as to the

transmitting agent, and there is hardly a biting parasite or insect which lacks an advocate.

The house-fly is thought by Row to be the carrier, chiefly on account of the coincidence of its seasonal prevalence with the most frequent period of infection at Cambay, and a similar view is expressed by Cardamitis and Melissidis, who support it by the results of some experiments in which they allowed *Musca domestica* to feed on a sore containing the parasites and believed that they got evidence of a certain degree of development of the parasites in the gut of such flies.

Phlebotomus has the support of Thomson and Balfour, and of Sergent (commenting on a paper by Cambillet), while Wenyon, who has made a very careful study of the question in Bagdad, also states that he is unable to exclude this insect.

Simulium has its advocate in Fink, and mosquitoes have frequently been suggested. In connexion with the latter, Wenyon quotes many facts observed by him at Bagdad pointing in the direction of *Stegomyia* as the possible carrier; among others, that he has by feeding experiments seen a certain degree of development of the parasite in the mid-gut.

Bugs cannot be said to have been altogether excluded, although the fact that they seldom bite exposed parts of the body is strongly against them. Thomson and Balfour suggest them, as an alternative to *Phlebotomus*, as the agent in the causation of the non-ulcerating form they found in the Sudan, and there is an interesting observation of Billet's of a man in Algiers who was bitten at night on the face by a bug, which he caught in the act, and who subsequently developed a sore at the exact spot.

It will be obvious from the above that we have still much to learn in connexion with the etiology of tropical sore and its possible relationship to kala azar. Nicolle and Manceaux sum up the situation well, speaking of the local reactions which sometimes result from inoculation of *L. infantum*, by saying, ' Aucune conclusion définitive ne pourra être portée avant que nous ne connaissions par quel hôte intermédiaire s'opère le transport des deux *Leishmania*, et que nous puissions par là même juger expérimentalement des caractères de la lésion locale d'inoculation, déterminée par chacun de ces hôtes avec chacun des deux virus.'

Treatment. In the past this has been notoriously unsatisfactory, there being no method which could be relied upon to produce rapid healing of the sores. It is fortunate that they have a natural though dilatory tendency towards spontaneous cure, but the average duration is about six months, and the scarring and pigmentation which they often leave behind them are very disfiguring. It is much to be hoped, therefore, that further trial may be given to some of the methods which have been recently advocated and for which better results are claimed.

The drastic procedure of excision of the sore has still its advocates, including Nicolas and Wenyon, but it is agreed that this should only be practised if the sore is single, and that it should be made to include apparently healthy tissue round the sore. If this is not done the sore may reappear in the cicatrix in a few days

as happened to Marzinowsky. The method has also the disadvantage that, if practised too soon, the individual is left without protection and may be re-infected. Free curetting should be carried out on the same principles and combined with the application of powerful disinfectants.

A new line of treatment has been recommended by Billet. The sore should be dusted with potassium permanganate, with the object of killing pyogenic organisms, and, a few days later, a 10 per cent. solution of methylene blue should be applied, with a view to the destruction of the protozoa. This method has also been found good by Nicolas, who recommends in addition the use of picric acid as an antiseptic, cicatrizant, and keratoplastic agent.

Another method is that of Gueyat, who advises that the crusts should be softened and the exudates eliminated by hot starch poultices kept on for 12–24 hours; next day the wound should be carefully cleaned of all débris with swabs and forceps and touched with oxygenated water or a 1 per cent. solution of permanganate of potash. This is repeated until the wound is perfectly clean, when the following ointment is applied, covered with dry gauze, and protected :—

Salicylate of methyl	5 grm.
Salicylate of bismuth	2 „
Subnitrate of bismuth	1 „
Oxide of zinc	20 „
Glycerin	10 „

Healing is usually very rapid, and he has never seen a case resist longer than three weeks.

Finally, Nicolle and Manceaux speak highly of the use of arsenobenzol. They tried it in two cases; to the first they gave 30 cg. with a partial improvement, and to the second 60 cg. with very rapid improvement.

In concluding this review of kala azar and tropical sore it has been thought well to deal separately with two points whose interest is common to each form of infection. These are, the demonstration of the parasite, and immunity.

The demonstration of the parasite. In tropical sore this is a matter of comparative ease; the lesion lies open to investigation and it is merely a question of a little experience and a satisfactory technique to stain and identify *L. tropica.* This is, however, far from being the case in Indian or infantile kala azar, and, however convincing the clinical picture, there can be no certainty of diagnosis until the parasites have actually been seen.

The means at our disposal for such demonstration are as follows: 1. Examination of the peripheral blood. 2. Vesication. 3. Spleen puncture. 4. Hepatic puncture. 5. Marrow puncture. 6. Cultivation. Each of these will be briefly considered.

1. *Examination of the peripheral blood.* The explanation for the general failure of this method in kala azar is twofold: the parasites, if present at all, are

very rare, and, since they are encountered in cells and not free, the intense leucopenia which is usually found adds greatly to the difficulties of the search. In the Indian form very few positive results have been mentioned, with the striking exception of Donovan's success at Madras; as already mentioned, he has demonstrated their presence in the peripheral blood in 93·2 per cent. of his recent Madras cases. On the other hand, Prashad records 213 examinations of finger blood with only one positive result, and the latter's experience is in accord with that of most observers. Donovan's technique, therefore, demands consideration and imitation. He compresses the pulp of the finger-tip for a minute before puncturing, in order to increase the number of the leucocytes, and then prepares several films in such a manner that the end of the film ends as a straight line and not in the customary ' tails '. The leucocytes will be found congregated in this zone, which facilitates their examination. Several slides should be searched exhaustively, and if negative the examination must be repeated at intervals of a day or two.

Nicolle and Comte advocated the collection of 1–2 c.c. of blood, which should be citrated and centrifuged, as in the usual opsonic technique, and the examination of the superficial layer of cells which contain an abundance of leucocytes. In a later communication, however, they record that this has yielded them no better results.

2. *Vesication.* The production of a blister by means of a vesicant applied to the skin was originally suggested by Cummins, and the writer is glad to take the opportunity of emphasizing this since it has erroneously been attributed to him by Nicolle and Comte. The object is to secure the examination of a larger number of leucocytes than can be done even by prolonged blood examination. It has not been very extensively tried, but several positive cases have been recorded in the infantile disease as well as in the experimental disease of the dog.

3. *Spleen puncture.* This is certainly the method most commonly in use and the most reliable one, but it has the grave disadvantage that it is not altogether free from danger. A certain number of instances of fatal haemorrhage have followed its practice, and these have led some workers to abandon it altogether. At the same time, many who have extensive experience of it consider it free from danger if certain precautions are observed. Nicolle and his colleagues have not mentioned any accident, Jemma and di Cristina have punctured 200 spleens and Bousfield 120 without trouble, and many others report similar favourable results. The following precautions should be observed : the spleen should be fixed as far as possible during a deep inspiration, if dealing with an adult; a fine, and preferably new, steel needle should be employed; both syringe and needle should be perfectly dry (to obviate haemolysis), and no more than a drop or two of blood should be taken—even if no blood appears to enter the syringe there will almost always be sufficient in the needle of the syringe to make films for examination. The operation should be carried out rapidly, and the syringe should not be held too tightly lest a sudden expiration should

threaten laceration of the splenic tissue. Pressure may be kept up with the finger on the site of puncture for a few minutes and the patient made to lie down for some hours. Preliminary treatment with calcium chloride is advisable if there is any reason to think that the blood is defective in coagulability.

4. *Hepatic puncture.* This method is recognized as being freer from risk than splenic puncture, but it has the disadvantage that it may yield negative results even when parasites are abundant in the liver. The syringe fills as a rule only too readily with blood, and it may safely be said of these operations, the more blood the less chance of finding parasites. What is desired is a fragment of hepatic tissue, and it is not easy to obtain this by simple puncture. At the same time, it is sometimes advisable to carry out hepatic puncture, and there is no objection to this provided that too much reliance is not placed upon a negative result.

5. *Marrow puncture.* This method, though largely employed in the case of experimental animals, has been little used in man. Donovan, however, in spite of his success with blood examination, advocates the perforation of the head of the tibia or of a rib with a small gimlet, which enables a sample of the marrow to be withdrawn for examination. An anaesthetic, however, is necessary, and the procedure does not appear free from danger.

6. *Cultivation.* This has been very little tried, but, in view of the ease with which cultures are obtainable from the spleen, at all events in the infantile disease, it might be more widely tried as a means of detecting parasites in the blood, when none can be found by direct examination. Novy, for instance, got a positive result in an infected dog when he failed to find parasites on microscopic examination.

Immunity. In common with other protozoal diseases we possess no precise knowledge of the nature of the immunity in *Leishmania* infections. That such immunity does occur has long been known in connexion with tropical sore, in which recovery results in a very marked and durable protection against subsequent infection; but the avenues of research which are open to us in investigating bacterial immunity are here closed or non-existent. Whatever changes occur in the tissues or fluids of the body in an immunized animal or man, we are not yet able to demonstrate or measure them by any of the methods used in bacterial investigations. Agglutination experiments with cultures are negative in their results, on account of the tendency of the parasites to spontaneous clumping, and experiments to demonstrate the presence of antibodies by complement deviation, using extracts of organs rich in parasites as antigen, have in Cannata's hands given negative results.

What information is available, then, has been derived from observation of the diseases in man and animals and from immunization experiments on animals. As regards natural immunity, acquired by a previous attack, this, as has been said, is a well-established fact in the case of tropical sore, and has also been borne out by experiments on dogs, where it has been proved by Nicolle and Manceaux that, after complete recovery from an experimental infection, the

animal is no longer susceptible. At the same time, they have found that it was not possible to induce this immunity by the inoculation intraperitoneally of large doses of the cultural forms. Apparently the monkey, when recovered from an experimental sore, has not attained a similar degree of immunity, since it has been found possible to re-infect it soon after the attack. For the establishment of this acquired immunity sufficient time must elapse, and attempted re-infections shortly after recovery, or before this was complete, have shown that there exists a degree of hypersensibility to infection.

Recovery is unfortunately so rare in human kala azar that we have little knowledge of natural acquired immunity in this instance. Still, cases undoubtedly do recover spontaneously, which proves that there must have been sufficient immunity produced in such cases to destroy the parasites and bring the disease to an end. The only observation as to the existence of such immunity is that of Muir, whose successful treatment of Indian kala azar has already been mentioned; he states that recovered cases are liable to re-infection but have a milder attack. It is open to doubt whether such cases were true recoveries and whether it may not have been possible that the disease was only in abeyance.

The part played by the phagocytic cells of the host is obviously one of great importance, and it appears legitimate to attribute to phagocytosis an important rôle in both protection and recovery from infection. It is evident that all forms of the parasite, flagellated as well as non-flagellated, are readily taken up by all cells which possess this power, and it is equally evident that these cells are, in most cases, unable to destroy them. The essential factor, then, in successful immunity may be an improvement in the activities of these cells, which enables them not only to ingest the parasites but also to destroy them by intracellular digestion. The writer has mentioned the experiments in which he observed *in vitro* phagocytosis of the flagellate forms of *Leishmania infantum* and their complete disintegration within human leucocytes, and this is quite consonant with the general failure to cause experimental infection by means of this stage of the parasite; it would be interesting to try similar experiments with the flagellate forms of *L. tropica*, with which experimental infection is possible.

Very interesting results have been obtained by Nicolle and his colleagues in cross-immunization experiments with *L. infantum* and *L. tropica*. They find that recovery from an attack of kala azar protects an animal against infection with the virus of tropical sore, and have also found evidence of some degree of immunity against kala azar in a monkey which had recovered from an experimental tropical sore. They have also numerous observations on the effects of passage of each of these viruses through dogs and monkeys upon the virulence of the strain, but the varying degrees of susceptibility of these animals naturally make them guarded in their conclusions.

The general trend of those experiments shows a close relationship existing between the different species, and it is possible that, with further experience,

we may be able to take advantage of this for prophylactic and therapeutic purposes.

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ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

THE FIFTH ANNUAL GENERAL MEETING was held in London on Friday, June 9, and Saturday, June 10, in the Institution of Electrical Engineers.

On Friday morning, June 9, Professor Glynn took the chair at 10 a.m. The minutes of the previous meeting were taken as read, and confirmed.

The Officers of the Association for the ensuing year were then elected as follows:—

President: Sir Thomas Barlow, Bt., K.C.V.O.

Treasurer: Dr. Hale White.

Secretary: Dr. Herringham.

Members for England:—

Dr. Judson Bury.
Dr. William Collier.
Professor Wardrop Griffith.
Dr. H. P. Hawkins.
Dr. R. Hutchison.
Professor Saundby.

Members for Scotland:—

Dr. William Russell.
Dr. W. K. Hunter.
Professor Stalker.

Members for Ireland:—

Dr. William Calwell.
Dr. O'Carroll.
Dr. A. R. Parsons.

The President mentioned that owing to the sad death of Dr. Alexander Bruce a vacancy was left in the representation of Scotland. He said that a Committee Meeting would be held that night and a fresh nomination would be made the following morning.

It was announced that the epidiascope in use had been kindly lent by Mr. Leitz, of 9, Oxford Street, for the occasion.

The following were then elected Members of the Association:—

Dr. James Carslaw, 6, Woodside Crescent, Glasgow.
Dr. Gordon Holmes, 58, Harley Street, W.
Dr. Frederick Langmead, 53, Queen Anne Street, W.
Dr. Thomas Lewis, 58 A, Wimpole Street, W.
Dr. Alfred Mantle, 62, York Place, Harrogate.
Dr. Alfred E. Russell, 7, Upper Wimpole Street, W.
Dr. Owen T. Williams, 42. Rodney Street, Liverpool

The Treasurer then presented his accounts

Showing a cash balance of   £175   0   5
And a deposit account of   400   0   0

Professor Wardrop Griffith then related two cases of Heart-block and also gave the details of a case of Thoracostomy.   Dr. James Mackenzie, Dr. Poynton, Dr. Hale White, Dr. John Cowan, Dr. G. A. Sutherland, and Dr. Travers Smith joined in the discussion.

Dr. James Mackenzie gave a communication on Nodal Rhythm and Auricular Fibrillation.   It was discussed by Dr. Gossage, Professor Osler, Dr. W. T. Ritchie, Dr. Melland, Dr. Rose Bradford, and Professor Hill Abram.

Dr. John Cowan spoke on the Association of Mitral Stenosis and Granular Kidneys. Dr. Herringham, Dr. Rolleston, Dr. Newton Pitt, Dr. David Lees, Dr. Parkes Weber, Professor Saundby, Professor Osler, and the President joined in the discussion.

Dr. Buchanan then spoke on Auscultation and Tuning-fork Vibration. Dr. Habershon, Dr. Hertz, and Professor Carter joined in the discussion.

Dr. McKisack then made a communication on Backward-pressure Phenomena in Heart Disease.

Dr. Nathan Raw showed two cases of Congenitally Diseased Heart, one from a woman aged 23.

The Session then adjourned.

At 2 p.m. demonstrations were given—

(a) By Dr. T. Lewis in the Medical School Buildings of University College Hospital on the String Galvanometer for registering cardiac movement.

(b) By Mr. Harmer at St. Bartholomew's Hospital on the method of bacteriological examination and vaccine therapy used by the Laryngological Department.

At 3 p.m. the Session resumed.

Dr. Head gave a communication on the Clinical Aspect of Lesions of the Optic Thalamus, and Dr. Gordon Holmes showed some sections illustrating the condition.

Dr. Byrom Bramwell related two cases of Great Constriction of the Fields of Vision due to bilateral Lesions of the Occipital Lobes in which the diagnosis had been subsequently verified by post-mortem examination.

Dr. Acland related a case of Acute Optic Neuro-myelitis, illustrated with many coloured drawings.   Dr. Sharkey, Dr. Hobhouse, Dr. Parkes Weber, and Dr. Ernest Reynolds joined in the discussion.

Dr. Hawthorne spoke on the significance of a Bilateral Extensor response in conditions attended with unconsciousness.   Dr. Parkes Weber, Dr. Newton Pitt, and Dr. Lister joined in the discussion.

Dr. W. K. Hunter related a case of Pseudo-bulbar Paralysis with a lesion in each internal capsule.   Dr. Ernest Reynolds, the President, and Dr. Byrom Bramwell joined in the discussion.

Dr. Buchanan described a new method of staining Erythrocytes, and showed certain bodies in the erythrocytes of a case resembling Henoch's purpura.   Dr. Byrom Bramwell spoke.

Dr. Parsons made a communication on the action of X-rays on Leucocytes in Myelogenous Leukaemia and showed that the uric acid output did not increase as the leucocytes diminished.

Dr. Hobhouse related a case of Spleno-medullary Leukaemia with a rapid fall in the number of Leucocytes.   Dr. Arthur Hall spoke.

Dr. Melland made a communication on Acute Leukaemia.

The Session then adjourned.

The Annual Dinner was held in the Connaught Rooms, the President in the Chair.

On Saturday morning. June 10, the Session opened at 10 a.m.

The President announced that the Executive Committee nominated Dr. William Russell to fill the vacancy in the Committee.   Dr. William Russell was elected unanimously.

Professor Osler spoke on the indications for, and the results of Splenectomy, relating six cases.   Dr. Fred. Smith, Professor Saundby, Dr. Rolleston, Dr. Parkes Weber, Dr. Sandwith, Dr. Peacocke, Dr. Hobhouse, Dr. Drummond, and Dr. Sutherland joined in the discussion.

Dr. Garrod spoke on Congenital Family Steatorrhoea.   Dr. Gossage and Dr. Craven Moore spoke.

Dr. Collier related a fatal case of Anaphylaxis.   Dr. Harry Campbell, Dr. Goodall, Dr. Newton Pitt, Dr. Rose Bradford, and Dr. Hay joined in the discussion.

Professor Hill Abram related a case of Actino-mycosis.

The Session then adjourned, several papers being, necessarily, left unread.

A Demonstration was given at 12 noon by Professor Keith in the College of Surgeons on Specimens illustrating Hypertrophy, Atrophy, Heart Disease, and Acromegaly.

At 2.30 a demonstration of living patients was held in the Examination Rooms of the Conjoint Board, at which over 50 patients were exhibited.

The Annual General Meeting then adjourned.

THE ADRENAL CORTEX, ITS RESTS AND TUMOURS; ITS RELATION TO OTHER DUCTLESS GLANDS, AND ESPECIALLY TO SEX

By ERNEST E. GLYNN

(From the Thompson Yates Laboratory, University of Liverpool)

With Plate 8

THE objects of this paper are :—(1) To classify and describe the commoner adrenal tumours upon a combined clinical and histogenetic basis. (2) To draw attention to the relation between the adrenal cortex and other ductless glands, and especially to sex characters. (3) To present new reasons against the hypothesis that renal hypernephromata are derived from adrenal rests.

It is advisable to recall certain facts which are now generally admitted concerning the development and physiology of the adrenals.

Development. (*a*) The adrenal cortex is developed from the Wolffian ridge, from the mesothelium of the mesoblast, that is to say, the same *Anlage* as the ovary and testis ; but the medulla is developed from the *Anlage* of the sympathetic ganglia, and is neuroectodermal in origin. (*b*) During foetal life the gland is at first larger than the kidney; even at birth they are nearly equal (Keith (43)). Its large size is the result of a peculiar hypertrophy of the inner portion of the cortex—the foetal cortex. This begins to degenerate immediately after birth, and the adult cortex is developed from a rim of smaller cells (Elliott (21)).

Physiology. It is universally admitted that the adrenal medulla and the rest of the chromaffin system, through the secretion of adrenalin, influence the blood-pressure.

The injection of adrenalin into animals also produces glycosuria, apparently with a diminution in pancreatic secretion (Pick and Glassner). Further, adrenalin glycosuria does not occur in thyroidless rabbits (Pick and Pineles (66)). This fact, among others, suggests some connexion between the chromaffin system and the thyroid (von Neusser (58)). Stoeltzner explains rickets and osteomalacia by functional insufficiency of the adrenal gland, and Bossi (12) claims favourable results in treating rickets with adrenalin (Kaufmann (42)).

The functions of the adrenal cortex are by no means as obvious as those of the medulla. Rolleston (73) mentions three views : (1) that it is connected with growth and development, especially of the sexual organs; (2) that it is antitoxic; (3) that it plays some part in the elaboration of the secretion of the

medulla of the gland adrenalin.[1] The occurrence of hypoplasia of the adrenal gland in anencephalic monsters suggests a connexion between the adrenal and development. Zander (107) has collected 42 such cases, but believes that the adrenal atrophy is secondary to the cerebral defects. It is generally stated that the hypoplasia affects both cortex and medulla equally. Elliott and Armour, however, have recently examined a case of anencephaly in a full-term child, and found that the medulla and the paraganglia were normal, but the foetal cortex was absent.

Swale Vincent (96), reviewing the question in 1910, concludes 'there is some evidence that the cortex furnishes a hormone which influences growth and nutrition, and especially the reproductive organs '.

As the cortex and medulla are developed from different *Anlage,* the growths originating from them must be subdivided. Simple hyperplasia has been included in this classification for the sake of simplicity, and because there is often no demarcation between it and a true neoplasm. Adrenal rests will be considered separately.

Benign Tumours.

(a) *Medullary Tumours. Group* 1. Hyperplasia, clinically often associated with increased blood-pressure ; thus Philpot (64) examined the adrenals in 21 cases of increased blood-pressure, and found enlargement of the medulla only, and in most an increase of the chromaffin substance.

Group 2. Glioma (Virchow) and, less common, Ganglion Neuroma (Weichselbaum), in which the symptoms are either entirely absent or not characteristic. The adenomata sometimes found in the medulla are probably always derived from the cortex (Thomas (90)).

(b) *Cortical Tumours. Group* 1. Diffuse hyperplasia, passing gradually into

Group 2. Adenomata, which may be bilateral (a variety described by Virchow as struma suprarenalis). The cells contain a considerable amount of fat, and their arrangement usually resembles that in the zona fasciculata.

Clinically 'adenomata are not uncommon in general arteriosclerosis with granular kidney' (Rolleston (72)).

Erwin Thomas (90), who has recently reviewed the relation between enlargement of the adrenals and granular kidney and arteriosclerosis, concludes that the cortex is more often hypertrophied than the medulla, and ' there is no reason to believe in any real relationship between cortical or medullary hypertrophy and a particular complex of morbid changes '.

Pseudo-hermaphroditism, almost invariably feminine, is associated with hyperplasia of the adrenal, probably of the cortex alone ; this will be alluded to later.

Malignant Tumours.

(a) *Medullary Tumours. Group* 1. Glio-sarcoma. Very rare. Kuster (46) has described two cases, one producing metastases.

Neusser and Weisel (58) believe the majority of these tumours arise, not from

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[1] Kawashima (119) recently claims to have found adrenalin or a substance closely allied to it in the cortex.

the neuroblast, but from formative cells of the sympathetic; they admit, however, the growths are malignant. It is not certain that all these tumours which occur in infants are sarcomata; Kretz and Weisel (see Neusser and Weisel, p. 93) maintain they are often derived from the embryonic sympathetic cells, while Schilder (80), 1909, regards them as malignant gliomata of the sympathetic, which may be recognized, if suitably fixed and stained, by their fine fibrillary ground substance and the glia balls.

Group 2. Sarcomata—'often resemble ordinary round-celled' (Adami). Neusser and Frankel have each described in young persons cases of hypertrophy of the left ventricle, and high blood-pressure, which they believe were due to increased functional activity of the chromaffin system from tumour formation, a sarcoma and angiosarcoma respectively. Six cases of melanotic carcinoma have been described; in one recorded by Davidsohn (19) a man, aged 58, died with symptoms of Addison's disease, the oral mucous membrane was pigmented, and the growths contained adrenalin.

(b) *Cortical Tumours.* There are two distinct groups of cortical malignant growths, viz. the sarcomata and hypernephromata. In children, at any rate, the difference is clinical as well as histological. Authorities disagree as to whether sarcomata arise from the cortex or medulla, or both. The larger bulk and greater amount of connective tissue in the cortex suggest that it is the commoner site. Such sarcomata must grow from the mesenchyma.

Group 1. Sarcomata, round-celled, often lymphosarcoma, i.e. small cells with an alveolar arrangement. These tumours are common in children, especially males between the ages of two and three.

Frew (28), who has collected 51 cases, states that when the growth arises in the left suprarenal 'secondary deposits occur in the liver, ribs, and cranial bones, and in the thoracic duct and certain of its tributaries', whereas in the right suprarenal growths 'secondary deposits are found on the upper surface of the liver, in both lungs, and, in a few cases, in the cranial bones, and also in the right lymphatic trunk and certain of its tributaries'.

Hutchison (117) first drew attention to the frequent occurrence of exophthalmos as a result of the skull metastases.

Ten out of thirteen cases examined microscopically (Tileston (91)) were sarcoma or lymphosarcoma, the others alveolar sarcoma, or endothelioma, melanotic cancer, and hypernephroma respectively. Frew (28), who has examined sections of seven other cases, states that 'the appearances are in all very similar'. The cells are round or oval in shape, about 6 m. in diameter, and appear to be made up chiefly of nucleus. The protoplasm is granular. 'There is a delicate supporting framework of long narrow cells, with spindle-shaped nuclei, the round cells being arranged in clumps in the spaces.' 'The secondary deposits show the same characters.' 'The appearance' was 'quite different to the case described by Bulloch and Sequeira (14) of carcinoma of the suprarenal cortex.' On account of the tendency to infect the lymphatics, Frew regards these tumours as more allied to carcinoma originating probably from the medulla.

Pepper (62) has drawn attention to the occurrence of sarcoma of the liver in infants, which is almost invariably associated with adrenal growths. The enlargement of the liver is enormous, and occurs congenitally, or in the first weeks of life. There is no ascites. The growth has a characteristic infiltrating appearance, and is invariably a small round-celled sarcoma. Eight cases have been published (Tileston). Case 22 in Frew's series of a child aged five weeks really belongs to Pepper's type, and is the ninth case.

Group 2. Adrenal Hypernephroma, or Mesothelioma. A tumour having large polyhedral, epithelial-like cells, recalling the structure of the suprarenal cortex (Kaufmann), alluded to in this paper as adrenal hypernephroma. The histological structure will be more fully described later.

Clinical Types in Children.

This tumour is almost invariably characterized in children by 'precocious growth of the body generally and of the sexual organs, with overgrowth of hair and fat. Pigmentation may occur, the skin being darker than normal, but not bronzed as in Addison's disease. Intellectually the children are often dull.' In 1905 Bulloch and Sequeira collected 12 cases, verified by post-mortem examination; I am able to add five more, making seventeen in all, and of these fourteen were females and three males. The tumours usually increase much more slowly than most other malignant growths. They do not all produce metastases. These cases have been further subdivided by Leonard Guthrie (36) into two:—(1) The obese type met with in both sexes; but, apart from the presence of pubic hair, the development of the sexual organs is not marked, though one of the females menstruated. (2) The muscular or 'infant Hercules' type, occurring only in males, who may show true sexual precocity.

The following case occurred under the care of Mr. Dun at the Liverpool Children's Infirmary:—

Lily D., aged 5, was admitted on Oct. 18, 1910, with abdominal tumour.
Apart from acne and seborrhoea her general health had been good up to the age of 3, when she began to complain of occasional abdominal pain and headache. Abdominal swelling, first noticed six weeks before admission to the hospital, had rapidly increased. The child walked at the age of 15 months and was bright and intelligent until a few weeks previous to admission, when she became dull and listless. The precocious development of the child was extraordinary. Her appearance was that of a girl abnormally tall, about the age of puberty. She was fat and flabby, and had a profuse growth of hair on the scalp, upper lip, pubes, and back. The mother had not noticed the abnormal growth of pubic hair. She had never menstruated. The skin was harsh and dry, with acne spots and seborrhoea on the face and shoulders, and there was no pigmentation. The abdominal swelling was due to an irregular tumour of varying consistency occupying the right half of the abdomen and bulging the lumbar region. The tumour moved on respiration. The respiratory, cardiac, alimentary, and renal systems were normal. On rectal examination the uterus appeared to be of the usual size, and no hypertrophy of the clitoris or mammae was present. The child was unable to stand, but there were no signs of paralysis. Intellectually she was dull and apathetic, took no interest in her surroundings, and would only answer questions when frequently repeated.

For the first two days in hospital her condition remained unchanged. On the third day the temperature, pulse, and respiration rates rose, and the child became semi-comatose, cyanosed, and had several severe convulsions. She died on the fourth day with symptoms and signs suggesting pneumonia. Owing to the child's unexpectedly sudden death, her height and weight were, unfortunately, not ascertained.

Post mortem. The left suprarenal capsule was present and of normal size in appearance, but the right could not be found. Situated, however, in the right lumbar region, and completely hiding the kidney, was an enormous oval tumour, weighing 2 lb. 12 oz. It measured $7\frac{1}{2}$ inches longitudinally, 5 inches transversely, and 4 inches antero-posteriorly; its long axis was in the long axis of the body. The kidney, somewhat flattened, was loosely embedded in an impression in the lower half of the tumour, to which it was attached by adhesions. The surface of the tumour was mainly a yellow-ochre colour, sometimes dark red. Portions of it were irregularly lobulated, the lobules varying from about $\frac{1}{2}$ to 3 inches diameter. On section the lobulation was more distinct, and the growth presented a variegated appearance, portions of it being yellow-ochre colour, while others were whiter from necrosis or dark red from the presence of blood. The tumour was more or less encapsulated, the kidney could be easily removed from it, and there was no infiltration of the adjacent tissues except into one small vein in the hilum of the tumour about $\frac{1}{8}$ inch in diameter; its wall was penetrated by a small nodular growth, verified microscopically; there were no metastases. The other organs were normal, except the lungs, which were very congested.

Portions of the tumour were preserved in Kohn's fluid, and frozen sections examined for chromaffin reaction—with negative results. Other portions treated with osmic acid showed a small quantity of fat in certain cells.

Five different pieces of the tumour were fixed in a mixture of formol, methylated spirits, and glacial acetic acid, and paraffin sections stained with haematoxylin and eosin, Van Gieson, and Mallory's aniline-blue connective-tissue stain.

Microscopically the tumour was composed of cells which vary considerably in shape and size, the majority polyhedral, many round or oval, a few spindle-shaped. Occasionally giant cells were present; these were irregularly round and sometimes oblong. The nuclei were relatively large, being round or oval and rich in chromatin, which was uniformly distributed. Mitotic figures, mostly atypical, were scanty. Some of the giant cells contained two or more nuclei.

The cytoplasm was usually homogeneous, but sometimes vacuolated. In one portion of the tumour this appearance was most marked, for in certain groups of cells the cytoplasm was full of small vacuoles, the nuclei central and small, and the general appearance and grouping with relation to the scanty stroma or blood-vessels closely resembled the zona fasciculata of the cortex of the left suprarenal gland, or of other normal suprarenal glands.

There was a delicate reticulum scattered here and there among the cells, and sometimes surrounding completely individual cells or groups of cells, producing a definite alveolar character. It is noteworthy that this reticulum was only satisfactorily demonstrated with Mallory's stain; in haematoxylin and eosin specimens it was almost invisible.

Blood-vessels were fairly numerous and usually composed of an epithelial layer only. The actual number of vessels, however, varied considerably. In a few portions, especially near the surface of the tumour, the vessels occupied at least half the microscopical field, forming a regular network, which surrounded slender columns of tumour cells. In other portions the vessels were almost completely absent; occasionally the tumour cells tended to group themselves round the vessels, recalling indefinitely a perithelioma; large and usually sharply

defined areas showed complete necrosis. The most striking feature of the growth was the variation in shape and size of the cells, and, to a much lesser extent, the variation in the number of small vessels and the amount of fine reticulum.

Conclusion. The absence of the right suprarenal capsule, the position of the tumour, its relation to the right kidney, and its general microscopical appearances prove that the growth is a true suprarenal one, while the groups of cells resembling the zona fasciculata and the absence of chromaffin indicate that it is in all probability derived from the *cortex* and not the medulla. Although metastases were absent, the infiltration of the small vein shows its malignant nature. The nomenclature of the tumour will be discussed later.

Microscopic examination of the other organs. Pancreas: Congested; Langerhan's areas unusually numerous and conspicuous, but no 'columnar hypertrophy'. *Liver*. A moderate degree of passive congestion, producing a slight nutmeg appearance. *Ovaries*: Normal. *Thyroid*: Markedly congested; epithelial cells more columnar than usual; the cytoplasm granular and its margins ill defined; the colloid material is reduced to about a quarter of the normal amount. The gland gives the impression of over-activity. *Left suprarenal gland*: Normal. *Pituitary body*: Normal; no excess of chromophil cells.

The following similar cases have occurred since Bulloch and Sequeira's (14) valuable paper:—

Drs. L. Guthrie and W. d'Este Emery (36) described a boy, aged 4¾ years, 36 inches high, who had had hair on the face and pubes for three years, and was as obese as a burly brewer's drayman in miniature. He died of acute tuberculosis. At the post-mortem the abdominal organs were thickly studded with tubercles; there was a rounded tumour the size of a large walnut in contact with the upper and anterior surface of the kidney. Neither adrenals could be found, in spite of careful search and a very complete microscopical examination of all the tuberculous and other material having any resemblance to these glands. The writers, therefore, concluded that the only adrenal substance present was that which occurred in the tumour itself.

Macroscopically the tumour was irregularly mottled, orange yellow, and chocolate. A histological examination showed masses of cells separated into alveoli of various sizes, the walls being formed in most instances by a network of slender blood spaces, occasionally by small bands of fibrous tissue. The size of the cells was extremely variable. Giant cells were occasionally present. In many the cytoplasm showed 'the foamy appearance seen in the cortical cells of the adrenal'. The authors regarded the growth as possibly a carcinoma, though it had grown slowly and not infiltrated or produced metastases. The ductless glands, including the pituitary, were normal on microscopical examination. The testes contained no spermatozoa. There was no tumour of the pineal gland. (Table I, Case 14.)

Dr. Walker's case (verbatim report by Dr. Owen Richards (75)). 'The patient, a girl, was healthy up to the age of 5, when she became very stout, and a growth of hair appeared on face, chin, and pubes. At 7 years this had grown to the average length of that of a man of 20, and the pubic hair was that of an adult. She then lost flesh on the face and limbs, her abdomen swelled, and a tumour was observed in the left hypochondrium. Slight albuminuria, no haematuria. Eighteen months later she was admitted to hospital. She then had the facial aspect of a young man of 20, with black silky beard and whiskers. Ascites was present, and she was tapped, whereupon the tumour and an enlarged liver became palpable. She died a few days later.

'*Post mortem.* Thorax was not examined. Liver enlarged and full of growth. Left kidney the size of a coco-nut, consisting entirely of new growth.

Right kidney about half this size and nearly destroyed by growth. Several mesenteric glands enlarged. Pelvic organs healthy and normally developed for the age. The adrenals were not mentioned.' (Table I, Case 11.)

Dr. Milton Miller (56) described in 1903 a case of 'abdominal tumour (sarcoma of kidney?) and pseudo-hermaphroditism in a child of 2 years. The subsequent history showed increasing dyspnoea, marked congestion of the face, profuse perspiration, luxuriant growth of pubic hair, and great abdominal enlargement. Death resulted from exhaustion eleven months later. A large tumour was found rising in the right suprarenal gland, with metastases in the liver, mesenteric glands, and right lung, microscopically a hypernephroma. The external genitals were moderately hypertrophied. The pubic region was covered with coarse hair. The labia majora were hypertrophied, and the labia minora projected from the vulva. The clitoris measured 4 cm., and the prepuce could be retracted. The ovaries were enlarged. There was no bronzing of the skin.'

Dr. Herbert French has kindly allowed me to allude to a case that recently came under his care. at Guy's Hospital. A girl developed pubic hair at the age of 18 months, and was admitted to hospital when 7 years old with hypertrophied external genitals and a large swelling in the left upper part of the abdomen, which from the symptoms and physical signs was diagnosed as an adrenal tumour. An operation was performed, and the growth which occupied the position of the adrenal was removed, together with the kidney to which it was firmly adherent. The kidney itself was entirely free from growth. The child died shortly afterwards with secondary deposits in both lungs. Obesity never occurred.

Dr. Herbert French kindly sent me a section of the primary growth, and of the metastases in the lung. They consist of round, oval, or, rarely, spindle-shaped cells with round or oval nuclei. The variation in shape and size is not so marked as in my case; multinucleated cells were very few. Part of the cytoplasm of certain cells was finely vacuolated. The stroma was scanty. In the primary growth, where necrosis was extensive, the cells had a definite tendency to be arranged radially round the vessels like a perithelioma, but this appearance was absent in the lung metastases. (Table I, Case 13*.) [2]

TABLE I.

Seventeen examples of Sex Abnormalities in Children associated with Adrenal Hypernephroma verified post mortem (modified from Bulloch and Sequeira, with five additional cases).

(The names in brackets are those of the observers.)

Case 1. (Bulloch and Sequeira.) F. **Age** at death, 11 ; at first symptoms, 10. **Hirsutes**: Chin, lip, axillae, pubes. **Nutrition**: Very stout, mammae. **Development of external sexual organs**: Menstruation. **Nature of tumour**: Hypernephroma 'malignum'. **Infiltration or metastasis**: Liver and lungs.

Case 2. (Colcott-Fox.) F. **Age** at death, 2; at first symptoms, 10 months. **Hirsutes**: Pubes. **Nutrition**: Enormous, bloated. **Development of external sexual organs**: Precocious. **Nature of tumour**: 'Large-celled sarcoma' (hypernephroma). **Infiltration or metastasis**: Lungs. **Remarks**: Dull.

Case 3. (Dickinson.) F. **Age** at death, 3; at first symptoms, ? **Hirsutes**: Pubes. **Development of external sexual organs**: ? **Nature of tumour**: ? **Remarks**: Dull, harsh voice.

[2] Photographs of the child will shortly appear in a book by Dr. Herbert French, entitled ' Index of Differential Diagnosis of Main Symptoms '.

Case 4. (J. Ogle.) F. **Age** at death, 3; at first symptoms, ? **Hirsutes**: Hair all over, moustache, pubes. **Nutrition**: Unusually stout. **Development of external sexual organs**: Well developed. **Nature of tumour**: 'Encephaloid cancer' (hypernephroma). **Infiltration or metastasis**: None. **Remarks**: Sullen, coppery but not bronzed skin.

Case 5. (Orth.) F. **Age** at death, $4\frac{1}{2}$; at first symptoms, 2 months. **Hirsutes**: Beard, pubes. **Development of external sexual organs**: Hypertrophy of clitoris. **Nature of tumour**: 'Carcinoma' (hypernephroma). **Infiltration or metastasis**: Liver and lungs.

Case 6. (Dobbertin.) F. **Age** at death, 1 year 2 months; tumour congenital. **Hirsutes**: Cheeks, back, pubes. **Nutrition**: Well nourished.

Case 7. (Tilesius.) F. **Age** at death, 4; at first symptoms, ? **Hirsutes**: Pubes. **Nutrition**: Enormous mammae. **Nature of tumour**: ? **Infiltration or metastasis**: Liver.

Case 8. (E. Cooke.) F. **Age** at death, 7; at first symptoms, ? **Hirsutes**: Face, pubes. **Nutrition**: Enormously fat. **Nature of tumour**: ?

Case 9. (Bevern and Romkild.) F. **Age** at death, $3\frac{1}{2}$; at first symptoms, $2\frac{3}{4}$. **Hirsutes**: Face, pubes. **Nature of tumour**: ?

Case 10. (Ritchie.) F. **Age** at death, 4. **Hirsutes**: Pubes. **Nutrition**: Well nourished, but not obese. **Development of external sexual organs**: Precocious. **Nature of tumour**: 'Sarcoma with large cells' (hypernephroma). **Infiltration or metastasis**: None.

Case 11. (O. Richards.) F. **Age** at death, $8\frac{1}{2}$; at first symptoms, 5. **Hirsutes**: Beard, pubes. **Nutrition**: Very stout. **Development of external sexual organs**: Not unduly developed. **Nature of tumour**: ? **Infiltration or metastasis**: Liver, both kidneys.

Case 12. (Miller.) F. **Age** at death, 3; at first symptoms, ? **Hirsutes**: Pubes. **Development of external sexual organs**: Hypertrophy of clitoris. **Nature of tumour**: Hypernephroma. **Infiltration or metastasis**: Liver.

Case 13. (Dun and Glynn.) F. **Age** at death, 5; at first symptoms, 3. **Hirsutes**: Face, back, pubes. **Nutrition**: Moderately obese. **Development of external sexual organs**: Not unduly developed. **Nature of tumour**: Hypernephroma. **Infiltration or metastasis**: Infiltration of suprarenal vein. **Remarks**: Dull.

Case 13*. (H. French.) F. **Age** at death, 7; at first symptoms, $1\frac{1}{2}$. **Hirsutes**: Pubes. **Development of external sexual organs**: General hypertrophy. **Nature of tumour**: Hypernephroma. **Infiltration or metastasis**: Lungs.

Case 14. (Linser.) M. **Age** at death, 5; at first symptoms, $1\frac{1}{4}$. **Hirsutes**: Pubes. **Nutrition**: Weight and development of boy of 15. **Development of external sexual organs**: Precocious. **Nature of tumour**: Hypernephroma. **Infiltration or metastasis**: Infiltration of suprarenal vein. **Remarks**: Sexual activity.

Case 15. (Adams, Raymond Johnson.) M. **Age** at death, 16; at first symptoms, 10. **Hirsutes**: Beard, pubes. **Nutrition**: Great muscular development. **Development of external sexual organs**: Precocious. **Nature of tumour**: Hypernephroma 'malignum'. **Infiltration or metastasis**: Infiltration of liver.

Case 16. (Guthrie and d'Este Emery.) M. **Age** at death, $4\frac{3}{4}$; at first symptoms, 2. **Hirsutes**: Face, pubes. **Nutrition**: Enormously fat. **Development of external sexual organs**: Not unduly developed. **Nature of tumour**: 'Carcinoma'? (hypernephroma). **Infiltration or metastasis**: None. **Remarks**: Bright, precocious.[3]

A perusal of Table I indicates that hypernephromata of the adrenal in children are much commoner in females and also tend to increase the male primary and secondary sexual characters at the expense of the female; witness the occurrence of beards in several of the female children, the usual absence of menstruation and the hypertrophy of the clitoris, also the greater muscular development of the male children.

[3] Apert (110) mentions that Otto (1816) found hypertrophy of the genitals associated with hypertrophy of the adrenal.

Six examples of Adrenal Hypernephroma in Young Adult Females associated with Changes in Sex Characters.

17. Knowsley Thornton, cited by Richards (75):—A woman, aged 36, who was covered all over with black silky hair, and had to shave her face. An ovariotomy had been performed six years before. Knowsley Thornton removed the tumour of the adrenal, which could have been peeled off the kidney. It weighed some 20 lb., and, after various complications caused by an abscess which burst into the lung, the patient made a complete recovery, and wrote nine months later to say that she was now normal in appearance, had gained two stones in weight, and could walk or drive any distance. Unfortunately she died of intraperitoneal recurrence two years after the operation. The structure of the tumour 'reminded the observer of the structure of an adrenal'. (Table II, Case 17.)

18. 'In the museum of the Royal College of Surgeons there is a specimen (Bulloch, 3518) of a large tumour which had replaced the right adrenal body, found in a woman of 32, who suffered from mania and epileptic fits, and it is noted that her face and extremities were so thickly covered with hair that a razor had been used.' Menstruation was absent. Histologically the growth was a soft carcinoma, composed of elongated alveoli filled with large granular epithelial cells. The alveoli were separated by capillary vessels and a very scanty stroma. (Table II, Case 18.)

19. Thummin (89) and Bortz (11), independently and without reference to each other:—A girl aged $16\frac{3}{4}$ began to menstruate at 15, and continued regularly for one year. With the cessation she grew a beard and moustache, and hair also on the thorax and linea alba. The voice changed to the male type. She became very obese; the mammae were well developed. She died of plegmon of the hand. The external genitals were of the feminine type, the uterus measured 8 cm. externally and was normal, but the ovaries were small and hard, showing no trace of ovulation, neither macroscopically nor microscopically. The right adrenal contained two yellow nodular tumours the size of a cherry and the left was converted into a mass as big as a fist. Microscopically the right tumour consisted of round or polygonal epithelial cells in a network of capillaries; those in the left showed similar structure, but the meshes were wider and more irregular. A few larger cells, rich in chromatin and often multinucleated, were also present. The condition is described as typical of 'struma suprarenalis'. (Table II, Case 19.)

20. Winkler (104):—A girl (Fall VII), aged 16, who died from a tumour of the right suprarenal capsule, with metastases in the liver and lungs; the kidneys were not involved. He notes there was a 'profuse growth of black hair on the upper lip, and both breasts were extraordinarily little developed', also that the very small uterus, only 5 cm. long, together with 'the tubes and ovaries, lay deep in the small pelvis close behind the symphysis'. The normal size of the uterus is 7·4 to 8·1 cm. (Vierordt (95)). Microscopically the tumour consisted of cells uniform in shape and size, separated into acini by a scanty connective tissue resembling in type and arrangement those of the adrenal cortex. The cells were often perivascular, and in places the blood-vessels were dilated so that the tumour might be described as 'epithelioma suprarenalis cavernosum'. In the metastases the cells tended to become spindle-shaped. (Table II, Case 20.)

21. Goldschwend (31):—closely resembles Thummin's.

A woman, aged 39, the mother of five children, who had not menstruated for three years, suffered during the last four months of life from epigastric pain, and noticed an abdominal tumour which slowly increased in size. Simultaneously a moustache and whiskers appeared, also an abnormal growth of hair upon the abdomen. She was somewhat emaciated.

At the post-mortem a tumour, the size of a child's head, was found, arising from the left adrenal ; it was described as a 'malignant adenoma'.   There were metastases in the liver.   The uterus and ovaries were very small ; the condition of the breast is not mentioned.   The pituitary and pineal glands were normal.

22. Ogston, III.   M. C., a girl aged 16, apparently in good health, was found dead in bed in June, 1862.   She had never menstruated.   At the post-mortem neither the breasts nor the pelvis were developed.   The ovaries were exceedingly small and both full of small cysts ; the uterus was not bigger than that of a new-born child.   Both suprarenals were enlarged to half the size of the kidney. The cause of death was not discovered.   (Table II, Case 22.)[4]

I have included in Table II two cases in which, from their clinical resemblance to those just described, it is probable that the adrenal glands were also enlarged.

Alberti (5) :—A normally built girl, in whom menstruation was regular from 16 to 19, completely ceased menstruating at 20.   Simultaneously the body became covered with hair, a beard grew, the breasts, previously well developed, atrophied, the muscles, especially the deltoids and pectorals, hypertrophied, the voice became deeper, and the clitoris enlarged.

At the age of 23 she died from a twisted right ovarian tumour which was discovered shortly before death.   The tumour was the size of a man's head, and proved microscopically to be a 'simple cystoma-multiloc. pseudo-mucinosum haemorrhagically infiltrated'.   Some of the cysts contained epithelium mixed up with the blood, but there was no epithelium upon the cyst walls.   The left ovary was said to be normal, but this is impossible as menstruation had ceased.   There is no mention of the suprarenal glands, kidneys, liver, &c., and as far as can be gathered from reading the original article, the only internal organs examined at the post-mortem were the left ovary and uterus.   The ovarian tumour was certainly not a hypernephroma, but of the usual multilocular type.   Its occurrence, in my opinion, is a coincidence.   Taking these facts into consideration, also the similarity of this case with the preceding, it is probable that the suprarenal glands were the seat of a growth which was overlooked.   (Case A, Table II.)

Krafft-Ebing, quoted by Halban (37) :—A woman ceased menstruation at her thirtieth year.   Three months afterwards hair began to grow upon the face and chest, the breasts atrophied, and 'the voice, formerly soprano, became like that of a lieutenant!'   Psychic changes also took place : formerly pliant and gentle, she became energetic and somewhat aggressive.   The condition is described as Klimax Praecox.   The patient was still alive in 1892, one year after cessation of menstruation.   (Case B, Table II.)

TABLE II.

Occurrence of some Male Sex Characters in Adult Females, associated with Adrenal Hypernephroma in six Cases, conditions of Adrenals unknown in two Cases.

Case 17. (Thornton.)   **Age** 36.   **Hirsutes:** Covered black and silky, shaved.   **Menstruation:** ?   **Uterus:** ?   **Ovaries:** ?   **Breast:** ?   **Adrenal affected—nature of tumour:** Right, malignant, metastases.   **Microscopically:** Like adrenal.   **Remarks:** Hair disappeared after removal of primary tumour.

Case 18. (Bulloch.)   **Age** 32.   **Hirsutes:** Thick on extremities and face, shaved.   **Menstruation** : Ceased.   **Uterus:** ?   **Ovaries:** ?   **Breast:** ?   **Adrenal affected—nature of tumour:** Right, malignant.   **Microscopically:** Soft cancer, vascular.   **Remarks:** Very anaemic.

[4] This is an anomalous case, as the enlargement may have been hyperplastic instead of neoplastic.

Case 19. (Bortz and Thummin.) **Age** 17. **Hirsutes**: Chest, linea alba, moustache. **Menstruation**: Ceased at 15. **Uterus**: Normal. **Ovaries**: Atrophied, no ovulation. **Breast**: Well developed. **Adrenal affected—nature of tumour**: Left, small tumour; right, large tumour. **Microscopically**: Struma suprarenalis. **Remarks**: Voice changed, obesity.

Case 20. (Winkler, Case VII.) **Age** 16. **Hirsutes**: Profuse on upper lip. **Menstruation**: Probably absent. **Uterus**: Very small, 5 cm. **Ovaries**: ? **Breast**: Extraordinarily small. **Adrenal affected—nature of tumour**: Right, malignant, metastases. **Microscopically**: 'Epithelioma suprarenalis.'

Case 21. (Goldschwend.) **Age** 39. **Hirsutes**: Face and abdomen. **Menstruation**: Ceased at 36. **Uterus**: Atrophied. **Ovaries**: Atrophied. **Breast**: ? **Adrenal affected—nature of tumour**: Left, malignant, metastases. **Microscopically**: Malignant adenoma.

Case 22. (Ogston, III.) **Age** 16. **Hirsutes**: ? **Menstruation**: Always absent. **Uterus**: Much atrophied. **Ovaries**: Exceedingly small, little cysts. **Breast**: Atrophied. **Adrenals**: Both half the size of kidneys. **Microscopically**: ? **Remarks**: An anomalous case.[5]

Case A. (Alberti.) **Age** 23. **Hirsutes**: Face and body. **Menstruation**: Ceased at 19. **Uterus**: ? **Ovaries**: Tumour right, left normal. **Breast**: Progressive atrophy. **Adrenals**: Not examined. **Remarks**: Voice changed, clitoris enlarged.

Case B. (Krafft-Ebing, Halban.) **Age** 31. **Hirsutes**: Face and chest. **Menstruation**: Ceased at 30. **Uterus**: ? **Ovaries**: ? **Breast**: Progressive atrophy. **Adrenals**: Not examined. **Remarks**: Voice and manner changed, still alive.

Pseudo-hermaphroditism.

The occurrence of hyperplasia of the adrenal gland, or of accessory adrenals with some cases of pseudo-hermaphroditism, is another example of the association between the adrenal and sex.

The fact that the great majority of these cases occur in female pseudo-hermaphrodites, that is to say in females with the external organs of the male type, further illustrates the tendency of neoplasia or hyperplasia of the gland to be associated with the appearance of male characters in the female. This is all the more striking as in most of the females the hermaphroditism was advanced, for prostates were present. All the recorded examples of pseudo-hermaphroditism with adrenal enlargement are set down in Table III. I have excluded Mannec's case of pseudo-hermaphroditismus femininus completus, because the adrenals were not examined at the post-mortem; though Fibiger assumes they were enlarged. Important facts regarding the adrenal or accessory adrenal glands are given below, also clinical particulars of two cases from an inaccessible journal (Ogston I and II (59)).

Marchand (48). Table III, Case 24. The measurements of the two adrenals were—right, $7\frac{1}{2} \times 6 \times 2$ cm.; left, $8\frac{1}{2} \times 6 \times 3$ cm. No medulla was visible to the naked eye, while microscopically the gland was composed of cells resembling cortical cells in the usual vascular stroma, and there was no distinction between cortex and medulla. An accessory adrenal in the right broad ligament which was the size of a testicle had the same structure.

Engelhardt (24). Table III, Case 25. The right suprarenal was situated under the kidney, and formed a tumour about the size of a Borsdorfer apple (small apple); the left was normal; microscopically the tumour showed struma aberrans suprarenalis. There is no further description.

Fibiger, II (25). Table III, Case 27. The adrenals measured $8 \times 5 \times 3$. Microscopically the cortex immediately under the capsule contained almost

[5] Though the ovaries were not examined histologically in Ogston I, II, and III, the cystic condition of II and III proves they were not testicles.

normal zona glomerulosa passing into an imperfect zona fasciculata; in the rest of the glands cells resembling those of the cortex and medulla were mixed up together. But the actual demonstration of medullary cells was impossible as the tissue had been hardened in formalin, not bichromate.   Giant cells were also present.

Fibiger, III.   Table III, Case 28.   The right adrenal was $4\frac{1}{2} \times 3\frac{1}{2} \times 3\frac{1}{2}$, and left $4\frac{1}{2} \times 2\frac{1}{2} \times 3\frac{1}{2}$.   The cortex was furrowed like the surface of the cerebral hemisphere; microscopically the cortex and medulla can easily be distinguished, and both were of considerable depth, the different zones of the former quite obvious.   The small accessory adrenal in the left broad ligament, $3 \times 2 \times 2$ mm., is stated to have the same structure as that described by Marchand in Case II, p. 21.

Hepner.   Table III, Case 29.   This was originally described as hermaphroditus verus, Hepner believing that both testes and ovaries were present, but Meixner (54) has demonstrated that the former are without doubt two adrenal rests, one in each broad ligament.   The illustration shows that both zona glomerulosa and fasciculata were present (p. 328).   The adrenals themselves are not mentioned (see also Neugebauer, pp. 243, 244).

Ogston, I (59).   Table III, Case 32.   Mary Macintosh, aged 12, died from cholera in 1870.   At the post-mortem it was found that there was hair on the pubes and linea alba below the umbilicus.   The clitoris was enlarged to the size of a male glans penis.   The uterus was only a little bigger than that of a new-born child; the ovary was small but normal.   The suprarenals were enlarged so that each weighed 3 oz., but their appearance was normal.

Ogston, II.   Table III, Case 33.   Helen Macintosh, aged 5, died the same day as her sister, also of cholera.   There was hair on the pubes, and the external genitals were fully developed.   The clitoris was as large as a boy's penis.   The uterus was minute, and the ovaries small and covered with cysts.   The suprarenals were enlarged and weighed $2\frac{1}{2}$ oz. each.

Auvray and Pfeffel (112).   Table III, Case 34.   A tumour the size of a foetal head arose from the left adrenal, composed of polymorphic cells and often polynuclear giant cells, but not truly sarcomatous—' an adeno-angiolipoma '.   The remainder of the gland showed ' atypical glandular hyperplasia '.   The investigation demonstrated that the ' neoplastic disorder ' dated from ' embryonic life '. The right adrenal was enormously hypertrophied, but it was not examined microscopically.

Meixner.   Table III, Case 35, in a new-born infant.   This is unusual, being pseudo-hermaphroditus masculinus, instead of femininus.   There was double crypt-orchidism and three other round bodies, two near the right testicle 2·5 and 4·6 mm., and one near the left 6 mm. in diameter.   Microscopic examination proved that these bodies were adrenal rests, which contained the three cortical layers.   The illustrations indicate that the rests were much smaller than the testicles.   In the centre there were also a few cells with intensely staining protoplasm, which some authors describe as medullary substance.   The suprarenals themselves were normal in size; microscopically the cortex was abnormally vascular, a haemorrhage had occurred in one; the medulla was very scanty.

The evidence indicates that in pseudo-hermaphroditism the adrenal hyperplasia involves the cortex mainly, perhaps entirely; for the rests, as almost invariably obtains, consisted of cortex alone.   Hyperplasia of the medulla was never satisfactorily demonstrated, as bichromate fixation was not employed.

Though it is highly probable that the existence of adrenal hyperplasia in pseudo-hermaphroditism is often overlooked, yet it is clear that the association between it and sex characters is not nearly so close as in adrenal hypernephromata of children or young adult females.

TABLE III.

Thirteen examples of the Association of Pseudo-hermaphroditism, particularly Feminine, with Bilateral Hyperplasia of the Adrenal Gland or of Adrenal Rests (modified from Fibiger's Table with some additional cases).

Case 23. (Crecchio.) F. **Age** 45. **External genitals**: Male type; prostate present. **Distribution of hair**: Male type. **Pelvis** and **Breast**: Male type. **Condition of ovaries**: Fibroid, only one follicle (Mic.). **Adrenal glands**—Macroscopical: Both size of kidneys. Microscopical: ? **Remarks**: Pseudo-hermaphroditus completus.

Case 24. (Marchand, Gunckel.) F. **Age** 48. **External genitals**: Male type; prostate present. **Distribution of hair**: Male type. **Pelvis** and **Breast**: Male type. **Condition of ovaries**: No follicles, but doubtful remains (Mic.). **Adrenal glands**—Macroscopical: Right, $7\frac{1}{2} \times 6 \times 2$ cm.; left, $8\frac{1}{2} \times 6 \times 3$ cm. Microscopical: Cortical hyperplasia, medulla not noted. **Adrenal rests**—Macroscopical: Right broad ligament, size of testis. Microscopical: Cortical hyperplasia, medulla not noted.

Case 25. (Engelhardt.) F. **Age** 59. **External genitals**: Male type; rudimentary prostate. **Distribution of hair**: Male type. **Pelvis** and **Breast**: Female type. **Condition of ovaries**: Few imperfect follicles (Mic.). **Adrenal glands**—Macroscopical: Right, size of an apple; left, normal. Microscopical: Struma suprarenalis.

Case 26. (Fibiger, I.) F. **Age** 58. **External genitals**: Male type; prostate present. **Distribution of hair**: Male type. **Pelvis**: Intermediate. **Breast**: Male type. **Condition of ovaries**: No follicles, a trace of ovulation (Mic.). **Adrenal glands**—Macroscopical: Both very large. Microscopical: ?

Case 27. (Fibiger, II.) F. **Age** 47. **External genitals**: Male type; prostate present. **Distribution of hair**: Male type. **Pelvis** and **Breast**: Male type. **Condition of ovaries**: One follicle, no trace of ovulation (Mic.). **Adrenal glands**—Macroscopical: Both $8 \times 5 \times 3$ cm. Microscopical: Cortical hyperplasia, giant cells, some medulla-like cells.

Case 28. (Fibiger, III.) F. **Age** 6 weeks. **External genitals**: Male type; prostate present. **Condition of ovaries**: Normal (Mic.). **Adrenal glands**—Macroscopical: Both size of kidneys; right, $4\frac{1}{2} \times 3\frac{1}{2} \times 3\frac{1}{2}$ cm.; left, $4\frac{1}{2} \times 2\frac{1}{2} \times 3\frac{1}{2}$ cm. Microscopical: Cortex and medulla of considerable depth. **Adrenal rests**—Macroscopical: Left broad ligament, $3 \times 2 \times 2$ mm. Microscopical: Cortical hyperplasia, like Marchand's case.

Case 29. (Hepner.) F. **Age** 2 months. **External genitals**: Male type; prostate present. **Condition of ovaries**: No follicles (Mic.). **Adrenal glands**—Macroscopical: Apparently normal. Microscopical: ? **Adrenal rests**—Macroscopical: One in each broad ligament, the size of testis. Microscopical: Cortical hyperplasia, two zones present.

Case 30. (Krokiewicz.) F. **Age**: New-born. **External genitals**: Male type; prostate present. **Condition of ovaries**: Normal (Mac.), ? (Mic.). **Adrenal glands**—Macroscopical: Both size of kidneys. Microscopical: Pseudo-hermaphroditismus, incorrectly described as ' completus '.

Case 31. (Neugebauer.) F. **Age**: New-born. **External genitals**: Male type; prostate? **Condition of ovaries**: Normal (Mac.), ? (Mic.). **Adrenal glands**—Macroscopical: Enormous hyperplasia of both.

Case 32. (Ogston, I.) F. **Age** 12. **External genitals**: Hypertrophied clitoris. **Distribution of hair**: Male type. **Condition of ovaries**: Atrophied (Mac.), ? (Mic.). **Adrenal glands**—Macroscopical: 3 ounces each. Microscopical: ? **Remarks**: Precocious hirsutes, uterus atrophied.

Case 33. (Ogston, II.) F. **Age** 5. **External genitals**: Hypertrophied clitoris. **Distribution of hair**: ? **Condition of ovaries**: Atrophied (Mac.), ? (Mic.). **Adrenal glands**—Macroscopical: $2\frac{1}{2}$ ounces each. Microscopical: ? **Remarks**: Precocious hirsutes, uterus atrophied.

Case 34. (Auvray and Pfeffel.) F. Age 72. **External genitals**: Male type; prostate? **Distribution of hair**: Male type. **Breast**: Male type. **Condition of ovaries**: Atrophied (Mic.); no Graafian follicles. **Adrenal glands**—Right enormously hypertrophied; large tumour of left (Mic.). Adeno-angiolipoma; atypical glandular hypertrophy of remainder of gland.

Case 35. (Meixner.) M. **Age**: New-born. **External genitals**: Female type; prostate absent. **Condition of ovaries**: Normal infant testicle (Mic.). **Adrenal glands**—Macroscopical: Normal. Microscopical: Cortex vascular, medulla scanty. **Adrenal rests**—Macroscopical: Two in right broad ligament, 2·5 mm. and 4·6 mm.; one in left, 6 mm.; all much smaller than the testicles.

Classification. The cases given in Tables I, II, and III may roughly be divided into two groups:—

Group I. Acquired sex abnormalities with unilateral neoplasia. The adrenal enlargement is unilateral, microscopically neoplastic; it often produces metastases and directly or indirectly causes death, but growth takes place more slowly than most malignant tumours. The growth and its associated physiological and anatomical defects are most probably acquired (vide Tables I and II).

Group II. Congenital sex abnormalities, i.e. pseudo-hermaphroditism, with bilateral hyperplasia. The adrenal enlargement is bilateral, microscopically hyperplastic. Metastases are absent, though rests may occur, and death is due to other causes. The adrenal lesions and their associated physiological and anatomical defects are most probably congenital (vide Table III).

The line of demarcation between these two groups, however, is not complete, for some of the cases are intermediate. Thus in Group II the tumour was unilateral in Engelhardt's (24) case and locally neoplastic in Auvray's; in Hepner's the adrenals were apparently normal, but rests were present. The two girls, aged 5 and 12, described by Ogston, showed precocious development of the hair, and a degree of external pseudo-hermaphroditism as indicated by clitoris hypertrophy no more extensive than that obtaining in Orth's and Miller's cases (Group I), in which the adrenal lesions were unilateral and truly neoplastic.

In Group I the tumour was congenital in Dobbertin's, and bilateral in Thummin's case, while in Ogston's III both adrenals were apparently hyperplastic, and the description of Bulloch's also suggests hyperplasia rather than neoplasia (vide also his illustration). Again, there was ovarian atrophy in many of the cases of Group II, but it also occurred in three and probably in two other cases in Group I.

Microscopical Structure of Adrenal Hypernephroma.

The malignant hypernephroma of the adrenal has the following structure. It is a growth whose general appearance recalls in a great or less degree the adrenal cortex. It consists mainly of round, oval, or polyhedral—but never cylindrical—epithelial-like cells, usually varying considerably in shape and size. The cytoplasm may be finely vacuolated or foamy from the presence of fat or

doubly refractive material, myelin; but it is never dropsical. The nuclei are round or oval; sometimes multinucleated giant cells are present. Unless the anaplasia is great, the cells are separated into alveoli or columns by a varying amount of delicate connective-tissue stroma or of thin-walled blood-vessels, upon whose walls they directly abut; they are sometimes arranged in a perivascular manner. The general arrangement of the cells, connective tissue, and vessels suggests more or less completely the zona fasciculata, and the growth is of a carcinomatous type. In other tumours, or even other portions of the same tumour, the cells are more spindle-shaped, and the general appearance is that of a sarcoma of a mixed celled or large round-celled type with many giant cells. It may be very vascular.

This variability in structure has given rise to considerable confusion in nomenclature. They are described as sarcoma and malignant hypernephroma [6] (Kaufmann (42)); alveolar sarcoma (Beneke (9)); perithelioma, i. e. angio-sarcoma (Rolleston and others); malignant adenoma, i. e. carcinoma (Ribbert (74)); mesothelioma (Adami (1)); suprarenal epithelioma (Marchand); hypernephroid tumour (Lubarsch (49)). This confusion is in some degree due to different terminology employed by different observers to describe the same microscopical appearance, but it seems mainly to be the result of the following causes:—

As already mentioned the specific cells of the cortex are developed from mesothelium, which is itself developed from mesoblast. Now, Adami and Woolley (105) have pointed out, it is quite natural in a malignant growth from such tissue with marked anaplasia that the epithelial (i. e. mesothelial) characters and arrangement of the cells should revert to a more primitive sarcomatous (i. e. mesoblastic) type. Hence it is that different tumours of the same origin and different portions of the same tumour may vary in their microscopic appearances.

A good example of this reversion is Woolley's case, in which 'the primary growths originating in the adrenal cortex show the adenomatous and epithelial characters, and in the metastases a somewhat alveolar type of round-celled sarcoma verging towards spindle-celled'.

The occurrence of glandular structure with lumena is disputed. Many writers, as Bruchanow (13), Woolley, Lasagna (47), do not allude to it. Ribbert believes that true gland formation does not occur, but false lumena may arise from destruction of the central masses of cells (p. 431).

Stoerk (84) concludes from his investigations upon the adrenal cortex of man, the cat, the dog, and the rabbit that true lumen formation is absent in physiological and pathological conditions, viz. hypertrophy and adenoma.

Zehbe (108), the most recent writer on the subject, also denies the occurrence of true lumen formation, and mentions also that Poll, working upon the development of the suprarenal in vertebrates, never alludes to lumena. Marchand (52), however, states lumena are present in the suprarenals of horses.

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[6] This term is objectionable because such tumours are not always malignant and it does not distinguish them from 'renal' hypernephromas.

Manasse described true lumen formation in a small adrenal tumour (Case 25). Askanzi (7) also described a similar appearance, but as there was a large tumour in the kidney as well there is no proof that the primary growth did not arise there. The same remark applies to Kelly's case (No. 2) (44) of growth in the left adrenal; for although the kidney was normal there was also a mass of growth in the retroperitoneal tissue and the pouch of Douglas, and other growths in the lungs and mucous membrane of the bladder.

Dobbertin also described an unusual gland-like appearance, which will be alluded to later.

Comparison of the Microscopical Characters of the various cases of Adrenal Hypernephroma associated with Sex Abnormalities.

Macroscopically, according to Borst (10), the malignant suprarenal tumour is a 'lobulated haemorrhagic growth, necrosing in parts, of soft, fatty, butter-like consistency'. The variegated appearance so characteristic of our tumour is also noted in those described by Bulloch, Adams (3), Guthrie, and Dobbertin. Fox's (27) tumour was soft, with areas of haemorrhage: Dobbertin's nodular. There is practically no description of the macroscopic appearances in most of the other cases.

Microscopically these tumours show differences in structure only to be expected from their complicated histogenesis, the variation in the degree of anaplasia, and in their duration in years. Fortunately I have had the opportunity of comparing microscopical sections from Dun's, Ritchie's, Adams's, and French's cases, and am convinced that there is no essential difference between them, or between them and the other cases described.

In the variable nature of the polyhedral cells, in the occurrence of multi-nucleated giant cells, and in the presence of a vascular stroma, Dun's case is identical with Ritchie's, and, from the descriptions, with Orth's, Guthrie's, Fox's, and Thummin's. Other portions of Dun's case resemble Adams's; [7] in his, however, the stroma is more conspicuous owing to shrinkage from delay in fixation. The tendency of the cells to be arranged perivascularly is especially marked in French's and Winkler's cases, and slightly in Adams's and portions of Dun's.

In Bulloch's tumour the anaplasia was slight, for the cells varied little, and the resemblance to the zona fasciculata was striking. Dobbertin's tumour is of the same type as the others described, except that some portions show an 'exquisite gland-like structure' formed by one or two layers of cubical or polymorphous cells surrounding lumena containing irregular intrapapillary growths, desquamated cells, and granular débris.

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[7] In the original description of this tumour it is stated that one portion of the section is separated from the main mass by a 'broad band of dense connective tissue'. In this portion here and there one can recognize a small lumen which frequently contains a yellowish green mass of pigment. In my opinion, after examining the sections, this portion is hyperplastic liver tissue, the 'broad band' of fibrous tissue separating it from an adrenal tumour.

There is no doubt, therefore, that all the tumours associated with changes in sex characters are *essentially similar*, though the degree of anaplasia and the amount of sarcomatous-like tissue vary considerably. True gland formation with lumena is most probably always absent.

Adrenal hypernephroma is quite different histologically from adrenal sarcoma. Through the kindness of Dr. Frew I had the opportunity of examining microscopical sections of four of his cases of adrenal sarcoma in children, and comparing them with four cases of malignant hypernephroma in children, viz. Dun's, Ritchie's, French's, and Adams's. There is no resemblance whatever between the two groups. The failure of some writers to recognize two common and distinct varieties of primary malignant growths is probably due to the confusion arising from the tendency of hypernephroma to revert to its more primitive sarcomatous, that is to say mesoblastic, type (Figs. 1–4 and 5–8).

Age, Sex, and Frequency of Primary Malignant Tumours.

Rolleston and Marks (73) collected 15 cases of primary sarcoma, 8 in males, 7 in females; and 9 of carcinoma, 3 in males, 6 in females. Ramsay (70) found 66 cases of primary malignant adrenal growth had been recorded up to 1899, but it is by no means certain that they were all primary in the adrenal; 37 are described as sarcoma, presumably round-celled, but the author concludes, 'These figures are not of much value. Some tumours classified as carcinoma were undoubtedly sarcomata, and probably vice versa.' Of 62 cases, 36 were males and 26 females, though 15 were under 20 years of age. Woolley (105) collected only 22 cases of primary carcinomatoid adrenal tumours, and excluded a large number in Ramsay's series. 3 were female children, 11 men, and 8 women—4 of the latter were between 49 and 66. Hartmann (39) collected 27 cases of sarcoma and 16 of carcinoma; his figures include those of Rolleston and Marks. Richards described 12 new cases. Of these, 3 appear to be carcinoma, 2 male and 1 female adult; and 5 small round-celled sarcoma, 3 male and 2 female children; 4 were not examined. Winkler (104) published 3 new cases of sarcoma, 2 in male children and 1 in an adult male; and 10 of carcinoma, 6 in men and 4 in women, but in 1 woman and 2 men the kidneys were involved, and the growth may have been primary in them. Frew has collected 51 cases of round-celled sarcoma in children—sex not always stated, but 16 were females and 27 males. My figures of adrenal hypernephromata consist of 3 male and 14 female children, or with Bruchanow's case, 15 females.

The following conclusions emerge from these rather conflicting figures:—(*a*) Primary malignant adrenal tumours are very rare. (*b*) Sarcomata are commoner; more frequent in children, especially male children. (*c*) Adrenal hypernephromata are five times as common in female as in male children, though in adults they are slightly more frequent in males.

*Cortical Enlargement is not invariably associated with Changes in
Sex Characters.*

It is necessary to inquire whether neoplasm or extensive hyperplasia of the adrenal cortex can occur, in children or adult females, unassociated with precocious growth, with pseudo-hermaphroditism, or with the development of male characters at the expense of the female.

Adrenal hypernephroma in children. I found only one case which was not associated with precocious development. Bruchanow (13) described a medullary carcinoma of the right adrenal which also infected the hilum of the kidney in a girl of 14 months. The cells, though small, were very irregular in shape and size, and the cytoplasm often contained fat; the stroma was vascular. There is no mention of anything abnormal in the development of the child, but Bruchanow specially states that no clinical history whatever was available. We do not know, therefore, whether the growth was congenital, as in Dobbertin's case of a girl of the same age, in which precocity was present.

Adrenal hypernephroma in adult females before menopause. I have found four or five definite cases without changes in sex characters, though in the first two menstrual disturbances occurred.

1. Marchand (52), Case IV. Girl, aged 20, died of a tumour which 'undoubtedly originated in the right adrenal'; microscopically it consisted of large polymorphic cells, often multinucleated giant cells, and also smaller round polyhedral cells lying in more or less fibrous tissue containing widely extended blood-vessels. The growth, although very malignant, had a strong resemblance to adrenal tissue, and from the description and illustrations it resembles the ordinary type of malignant hypernephroma. The clinical description is good. She was ill a 'long time'; menstruation became irregular.

2. Owen Richards, Case LIX. Describes a female, aged 30, who died from a tumour which apparently arose from the right adrenal. Both kidneys were normal. Microscopically the growth was very vascular and consisted of 'masses of cells' with very little fibrous tissue between them'. The illness was of four years' duration; menstruation ceased six months before death.

3. Manasse (51), Case XXVIII. A woman, aged 43, died from a primary malignant growth of the right adrenal with metastases in the liver and bone. Microscopically it had an exquisite cancer structure composed of round polyhedral cells of a definite epithelial type lying in a fibrous stroma with some blood-vessels. The growth had no resemblance to normal adrenal tissue. No clinical history given.

4. Hartmann (39), Observation II. Marie L., aged 41, ill a year and a half. A large tumour of the left suprarenal capsule was removed by operation. The patient died next day. There is no statement regarding menstruation. Both kidneys, the right adrenal, and the internal genital organs were normal. There were no metastases. Microscopically the growth consisted of cubical or polyhedral epithelial cells with a considerable amount of fatty infiltration of their protoplasm. There were numerous haemorrhages.

5. Winkler, Case IX. A female, aged 48, died from a growth in the right suprarenal with metastases in the brain, after six months' illness. Microscopically there was a perivascular arrangement of the epithelial cells which 'agreed with the structure of the suprarenal'. Menstruation is not mentioned nor anything abnormal in the sexual characters; the duration of the illness was short, viz. six months.

Mouisset et Chalier (120) describe a primitive bilateral cancer of both adrenals, with metastases in the kidney and elsewhere, in a woman of 22 with no sex changes. The growth was not an adrenal hypernephroma, for the epithelial cells were always homogeneous, and often arranged like the ' epithelium of a tubular gland '.

Winkler also describes an epithelial growth in a girl of 19, and Weiss (99) (Case II) another in a woman of 27, but there is not sufficient evidence that they were primary in the adrenal, for the kidney was involved in both.

Turquet and Weinburg (92) describe a carcinoma of both adrenals in a female, aged 36, with no unusual clinical history, but as there were also growths in the lungs and brain and the adrenal tumours were *not* examined microscopically, the case is of no value.

Adrenal hypernephroma in adult females after menopause. Ramsay met with three primary adrenal tumours in women over 52, microscopically resembling adrenal hypernephromata, and Woolley alludes to five other cases (carcinomata). Changes in sex characters were not recorded.

So far as I can ascertain, there is *no essential histological difference* in the adrenal hypernephromata of children or adult men or women, whether they are associated with abnormal sex characters or not.

Adrenal Rests.

We have already seen that, as far at least as pseudo-hermaphroditism is concerned, there is some association between adrenal rests and development of sex characters. As is well known, rests are said to produce neoplasms; the so-called hypernephroma of the kidney is the commonest example.

We must now ascertain (1) whether adrenal rests or the tumours said to originate from them, particularly renal hypernephromata, are associated with abnormalities in growth or sex characters ; (2) whether such tumours, especially the common renal hypernephromata, have the same microscopical structure as the adrenal hypernephromata.

Extra-renal adrenal rests. These are comparatively common in certain localities, leaving the kidney out of consideration. Wiesel (102) found small nodules consisting of all three cortical layers in the neighbourhood of the epididymis in 76·5 per cent. of new-born male children ; they sometimes persist throughout, though in a less typical form. Schmorl (81) describes rests in four livers out of 510, varying in size from a pin's head to a pea, in which all three cortical layers were present. According to Neusser he found rests in 92 per cent. of cadavers, most frequently on the under surface of the liver. Ulrich (93) describes cases of adrenal rests in infants in which nothing unusual was noted at the autopsy, but the rests were very minute, some the size of a grain of corn, and the adrenals were normal.

Hanau, cited by Neusser, found accessory suprarenals connected with spermatic veins or sex glands in 5·9 per cent. of children under five years. There is only one recorded instance of an adrenal rest *inside* the ovaries or testicle, viz. Vareldos and Rob Meyer respectively, who found one in a foetal testicle

(Vonwiller, p. 102 (97)). Rests have been also described by Ribbert in the pancreas ; by Nicholson in the transverse colon ; by Aichel (4) on the broad ligament and spermatic veins in 24 females, 12 of whom were infants, 7 children under four, and 5 adults (Picke (65)) ; by Chairi (16) in 2 adult men and 2 adult women, in whom they were the size of a pea or less (in the 2 men and 1 woman all three cortical zones were present) ; by Dagonet (17), one the size of a pea in the right ligamentum latum of a woman aged 32, and another smaller than a pea in the spermatic plexus of a male child, microscopically all three zones of the cortex were again present, as in a similar case described by Marchand. It is clear that adrenal rests are common in infancy but rare in adults, also that they are too small to produce any appreciable physiological effect.

Tumours of extra-renal adrenal rests. Hyperplasia and adenoma in these extra-renal rests are rare. Those occurring in pseudo-hermaphroditism have already been mentioned.

Schmorl found an adenoma in the solar plexus of one man the size of a hen's egg, and of a walnut in the solar plexus of another. Vecchi (94) describes a hepatic hypernephroma as large as a nut in a pregnant woman aged 29, but, unlike Schmorl's case, it does not really resemble the adrenal cortex.

Picke (Case IV), by way of contrast with Marchand's case of pseudo-hermaphroditism, described hyperplasia of an accessory adrenal with normal genitals in a woman aged 40, who died of phthisis. The tumour, the size of a walnut, was situated near the iliac artery, and had the usual structure of a 'Marchand' adrenal rest. The adrenals were normal.

Malignant growths. Peppera (61), Powell White (100), and Phillips (63) have described malignant epithelial tumours of the liver which they believe originated in adrenal rests. Phillips's case was the only one occurring in a female, her age being 40. These tumours, however, judging from the descriptions and illustrations (as pointed out by Stoerk in discussing Peppera's case), resemble neither tumours of the adrenal gland itself nor ordinary renal hypernephromata. It is more likely, in my opinion, that they are derived from the hepatic cells, especially as in White's case the tumour was pigmented with bile.

Weiss (Case II) has described the case of a girl, aged 17, who died of malignant tumour arising in the ligamentum latum in the neighbourhood of the ovary, said to have originated from an adrenal rest. There was nothing unusual in the clinical history. Microscopically the tumour consisted of small cells often arranged with indefinite lumena ; in places they were perivascular. The description and illustrations are quite unlike malignant hypernephroma of the adrenal.

Ovarian Hypernephroma. Vonwiller (1911) collected five cases of large Grawitzian tumours of the ovary, the ages being 18 (Sternberg), 26 (V. Rosthorn), 27 (Vonwiller), 51 (Picke, Case V), and under 45 (Peham). The descriptions and illustrations of the growths resemble renal hypernephromata rather than adrenal hypernephromata. There was nothing unusual in the clinical history of these cases.

Gaudier (29), however, has described an ovarian tumour, ' very probably

derived from an adrenal rest, possibly from a corpus luteum,' in a girl aged 5, in whom there was precocious menstruation and mammary enlargement.

Ten other cases of precocious menstruation in ovarian tumour have been recorded by Clement Lucas, Parkes Weber, Brohl, Hoffacker (3 cases, referred to by Guthrie), Genitz, Meurer, Reidel (referred to by Neurath), and Gaudier. These, unlike Gaudier's tumour, did not resemble ' hypernephroma ', some being cystic and some sarcoma.

Apert describes a syndrome of hirsutes, clitoris hypertrophy, and cessation of menstruation with cystic ovarian tumours.   He quotes—

1. Alberti (already described).

2. Duradonna (*Rev. de la Soc. Med. Argentina*) ; the symptoms began at 24, and a pedunculated serous cyst of the right ovary was removed.

3. Audain, a mulatto woman of 49, from whom two dermoids, of the usual microscopical appearances, and a parovarian cyst, were removed; the latter was so typical that it was not examined microscopically.

There is no evidence that the ovarian tumours in these cases differed from the ordinary type, which are not associated with sex changes.   On the other hand, there is no evidence that the adrenals were examined.

The so-called ovarian hypernephromata probably arise from the lutein cells, which, as Zander (107) points out, are like the cells of zona fasciculata of the adrenal cortex on account of the contained ' fat and doubly refractile substance '. Grouzdew (33) and others have actually described ovarian tumours arising from lutein cells.   It is fashionable at present to label many doubtful neoplasms as endotheliomata, or, if possible, hypernephromata !

While there is only one recorded instance of an adrenal rest *in* the ovary, they are frequently found near it, and Bovin has described a remarkable case of tumour *outside* the *ovary*, associated with changes in sex character of the usual type.

A woman gradually ceased menstruation in her nineteenth year, after the birth of her second child.   With complete cessation she grew a beard, and hair on the abdomen.   The breasts and genitals were normal.   At 28 a large tumour adjacent to the left ovary was removed ; the right ovary and uterus were atrophied.   Two months later menstruation recommenced, and continued regularly, but the beard persisted.   Microscopically the ovary showed atrophy.   The tumour was a hypernephroma and consisted of a network of capillaries surrounding groups of polyhedral mononuclear epithelioid cells whose cytoplasm was finely granular and often contained large fat vacuoles; there were numerous haemorrhages.

It is not clear whether this growth differs histologically from other ovarian ' hypernephromas ', but its position with relation to the ovary is significant.

Renal adrenal rests.   Adrenal rests in the kidney are described as small bodies, often multiple and bilateral, derived from the cortex, situated under the capsule or in the cortex, the latter position being the rarer.   It is generally assumed that such rests are common, but it is surprising how few have been actually described.   Neither Lubarsch (49), Kelly (44), Sabolotnow (76), Neusser, Winkler, Zeigler (109), nor Kaufmann give a single example which they have personally observed.

Two examples are described in the English pathological journals, viz. by

Newton Pitt (67), who found a subcapsular rest in a pair of kidneys consisting of cortex and a trace of medulla ; and by Targett (88), who found one at the lower pole of a kidney in a shallow depression under the capsule. Grawitz (32) and Manasse (Case XX) have each described a case where the rests showed two layers. Ribbert figures two in his textbook, one subcapsular consisting of one layer, the other intracortical, but, in my opinion, not resembling the adrenal cortex at all (Fig. 11, p. 75).   Borst also describes a case in which the nodules are sub-capsular and intracortical. Ulrich (93) has met with seven examples. In the first the whole of the adrenals were subcapsular ; Klebs and Rokitanski have each described a similar case. In the second a portion of the adrenal was sub-capsular, a smaller portion embedded in the kidney substance. Another example of this has been met with by Hanau and Grawitz respectively (Ulrich). In two other cases the rests were in the kidney ; microscopically they all contained zona fasciculata. Ulrich's last three examples were small rests, not verified microscopically, two being subcapsular and one in the kidney substance.

I have examined over 1,500 kidneys in the post-mortem room, and remember meeting with nodules resembling adrenal rests only in two instances. In both they were the same yellow colour as the cortex, and both on microscopical examination proved to be papillary cyst-adenomata.

Microscopical Structure of Renal Hypernephroma.

In view of recent discussion, it is important to compare the microscopical structure of renal hypernephroma with that of hypernephromata of the adrenal itself ; of course the round-celled sarcoma or lymphosarcoma is excluded. The Grawitzian hypothesis, that hypernephromata of the kidney are neoplasms of rests from the adrenal cortex, formerly attacked by Sudeck (86), has been vigorously assailed recently by Stoerk (125), 1907, Zehbe (108), 1910, Wilson and Willis (103), 1911.

The structure of the renal hypernephroma is complicated. It consists of large polygonal, often cylindrical, epithelial-like cells with round or oval nuclei ; the cytoplasm of the cells is clear from the presence of fat or of dropsical swelling. A smaller dark cell may also be present, its cytoplasm being granular and often obviously spongy, but it stains well (see Fig. 10).

The arrangement of the cells is also complicated ; they have been classified by Stoerk into two broad types, the solid alveolar, and the tubular perivascular. The former resembles a spheroidal-celled cancer in arrangement, and the general appearance is not unlike that of a sebaceous gland ; the latter that of a columnar-celled cancer, the acini being formed usually by a single layer of irregular cubical or columnar cells. The tubules lie in a vascular stroma, and in some cases papillary processes with a definite perivascular arrangement of the cells project into the lumena. These tubules contain desquamating epithelial cells, undergoing fatty and dropsical degeneration, and sometimes blood (see Fig. 11).

There is thus true gland lumen formation. According to Zehbe, who has recently examined 37 cases, 40·5 per cent. of the growths were of a solid type and 59·5 per cent. had lumen formation.

Microscopical differences between renal and adrenal hypernephromata. It is clear that the microscopical structure of these growths differs from that of adrenal hypernephromata, as Stoerk and Zehbe maintain.

An examination of the actual sections from Dun's, Ritchie's, Adams's, and French's cases, also the microscopical descriptions of those of Orth, Fox, Thummin, Goldschwend, Bulloch (Case 18), Bruchanow, Marchand (Case IV), and others, have convinced me that all these tumours are entirely different from the ordinary renal hypernephroma (see Figs. 1–4, 9–12, Plate 8).

The illustration of Bulloch's case is quite unlike the ordinary Grawitzian tumour, and he definitely states that the ' highly reticulated condition of the protoplasm which is so marked a feature of many hypernephromata was not apparent'. Guthrie also remarks that his tumour 'differed in several respects from the common renal tumours derived from suprarenal rests, notably in the absence of an appearance suggesting that the cells are budded off from the perithelial cells '.

The microscopical reports of the cases by Miller, Thornton, Linser, and Ogle are too scanty to be of value.

Winkler's case also differed from renal hypernephroma.   It is noteworthy that this writer, in his treatise upon suprarenal growth, gives a different classification for his ten cases of supposed primary epithelial tumours of the adrenal gland from that for the eleven cases of Grawitzian tumours of the kidney (see pp. 151, 363). Ribbert also recognizes a difference in the histology of the two classes of tumours, for in the renal hypernephromata there may be a gland-like arrangement of the cells to form lumena filled with blood, a condition which may be so marked that some mistake these growths for blood-vessel endotheliomata (pp. 435, 436). When, as rarely obtains, there is a true glandular growth he believes it originates in the kidney itself.   Neither Winkler nor Ribbert nor any other writer, so far as I am aware, definitely states that these two groups of tumours are identical.

Dobbertin, on the other hand, maintains that his case closely resembled many kidney tumours which originated from adrenal rests on ' account of its exquisite and papillary structure '; he gives no illustrations.   But as Ribbert has pointed out (p. 431), these lumena are artefacts; besides, the cells had not the characteristic dropsical appearance and the lumena contained no blood, as so frequently happens in renal hypernephromata.

Absence of Abnormal Sex Characters with Renal Hypernephroma.

Hypernephromata said to arise in the kidney are much commoner than those in the adrenal; thus Garceau (cited by Ellis (22)) collected 176 cases of the former, and Woolley only 22 of the latter. Ellis found in 163 hypernephromata

(157 were in the kidney, 3 in the adrenal, 2 in the liver, and 1 in the uterus); and Zehbe 37 in the kidney and 1 in the adrenal.

Although renal hypernephromata are rare in children—Garceau only alludes to 4—yet they are not very uncommon in adult females.

As far as I am aware there is no case on record of the association of renal hypernephroma with changes in sex characters except the doubtful one of Richards, Table I, Case 11. In this both kidneys were infected, which is unlike a primary renal tumour, and as there is no mention of the adrenal gland the kidney lesions might have been secondary to growths in them.

This absence of abnormalities in growth of sex characters is strong evidence against the Grawitzian hypothesis of the origin of renal hypernephromata from adrenal rests.

Bearing in mind this and other facts, already alluded to, it is remarkable that adrenal rests in the kidney, though comparatively rare, should produce such a common tumour as the hypernephroma, by far the commonest renal tumour, while on the other hand adrenal rests in other localities, though comparatively common, should, like the adrenal gland itself, so rarely produce tumours either benign or malignant.

Other Evidence of the Association between the Adrenal Cortex and Sexual Functions.

Stilling (83) found enlargement of the adrenals in male rabbits during the breeding season. He also discovered seasonal variations in the adrenals of frogs; during the summer the peripheral part of the cortex contained certain peculiar elements—'summer cells'—which atrophied when the sex glands began to enlarge and pairing took place in the autumn (pp. 193, 194). Aichel (4) noted the adrenals were very large in animals with well-developed sex organs or reproductive instincts, also an increase of the adrenals of birds and some amphibia during the breeding season. It is highly probable that a similar change occurs in human beings, but there are no recorded observations upon this point.' Such an enlargement, however, if it does take place, may explain the curious tendency of any hair or 'down' upon the face or body of women to increase in amount during pregnancy, first noted by Hegar and confirmed by Halban (38). In my opinion Halban wrongly explains this 'hypertrichosis graviditatis' by a protective action of the placenta.

Guieysse (35) found considerable enlargement of the adrenal, affecting especially the zona fasciculata, in pregnant guinea-pigs. According to Schenk (79) these results have been confirmed by Ciaccio and Da Costa. Gottschau (30) showed that the outer zone of the cortex in pregnant rabbits increased in thickness at the expense of the medulla and inner zone, but he found that the whole gland measured rather less in pregnant than in non-pregnant animals and males.

Theodossief, quoted by Thummin, removed the ovaries in dogs and found

enlargement of the suprarenal cortex, especially the zona glomerulosa; they were examined from three weeks to two months after the operation. Schenk (79) castrated 1 male and 11 female rabbits, and found in all enlargement of the cortex, especially the zona fasciculata. Soli found in guinea-pigs and rabbits there was an enlargement of the suprarenals after castration, but towards the end of the second month, it had entirely disappeared, and eventually the suprarenals became smaller than the controls. According to Cecca (16), both cortex and medulla enlarged after castration.

Schenk (78) in a second series of experiments proved that the amount of adrenalin in the suprarenals of castrated rabbits diminished rather than increased.

In retarded sexual development, or rapid loss of function, the suprarenals are sometimes considerably atrophied. Karakascheff (41) described a case of a female, the mother of two children, who ceased menstruation at 27 and died at 39. At the post-mortem there was practically no hair on the axillae or mons. The uterus and ovaries were very small and the suprarenals almost entirely absent. Wiesel describes a girl, aged 18, without hair on the axillae or mons; the mammary glands were not developed, and the genital organs infantile. Both adrenals were small; microscopically the cortex was normal; there was great atrophy of the whole chromaffin system. Wiesel described similar atrophy of the chromaffin system in a man with status lymphaticus, an observation which has been confirmed by other observers.

Changes occur in two other ductless glands, the thyroid and pituitary, which are strikingly similar to those just described. The thyroid is enlarged in pregnancy, often after castration in both sexes (Cecca (16), Tandler (87)), and is atrophied in sexual infantilism.

Many observers have noted that the anterior lobe of the pituitary enlarges considerably during pregnancy (Fischer, p. 82); also after castration in men, women, animals, and birds (Tandler, Fischera (110), Soli). The latter, however, found that in his castrated rabbits the thyroid occasionally enlarged instead.

The Association of Adrenal Hyperplasia and Hypernephroma with Male Sex Characters.

One curious feature has emerged from this discussion, viz. adrenal hyperplasia or neoplasia is associated with a diminution of female and an increase of male primary and secondary sex characters. The converse does not occur; for in males, on the contrary, the 'maleness' usually increases. Evidence supporting this view is as follows:—

I. *Twenty females* (14 *children*, 6 *adults*) showed (a) presence of hair on the face in 8 children, viz. 1, 4, 5, 6, 8, 9, 11, and 13, and in 5 adults. This is more significant as the women were young, from 16 to 39. (b) The absence of mammae in all except 2 cases in children, viz. 1 and 7. In these it may be due to general obesity, and not to true glandular hypertrophy,

especially as in Case 16, male, the general obesity was more marked about the mammae. There are not sufficient data with regard to the adult females. (c) The absence of menstruation in every instance except Case 1 among the children. Neurath (56) alludes to 55 cases of premature menstruation occurring before the end of the ninth year, and states that the onset is most common in the first part of the second year (p. 56). He also notes that development of the breast occurs almost without exception when menstruation begins after the first year. In the adults there was an absence or cessation of menstruation in four cases, probably also in Case 20, for the uterus was very small. (d) Hypertrophy of the clitoris in three cases, viz. 5, 12, and 13*. (e) Change of voice in Case 19.

In the remarkable cases of Alberti and Krafft-Ebing, in which male characters appeared, it is probable that the adrenals were enlarged.

II. *Three male cases* showed (a) Presence of hair on the face in two, viz. 15 and 16. (b) Great muscular strength in two, viz. 14 and 15. (c) Development of sexual functions in one, viz. 14.

III. *Pseudo-hermaphroditism.* The occurrence of adrenal hyperplasia in 12 females but only 1 male pseudo-hermaphrodite is additional evidence of the tendency of adrenal hyperplasia or neoplasia to be associated with an increase of 'maleness'. The significance of these figures is emphasized by the following considerations :—

(a) Masculine pseudo-hermaphroditism is much commoner than feminine. Thus Neugebauer gives 795 cases of the former in Table XXIV, and only 246 cases of the latter in Table XXV. In Table VIII he gives the necropsis upon pseudo-hermaphrodites, and by comparing the cases tabulated here with those in Tables XXIV and XXV, though there are a few slight discrepancies, I find that post-mortems were performed upon 143 male and 88 female pseudo-hermaphrodites. Of course the adrenal glands were not examined in every instance ; but taking the figures as they stand, I find that adrenal hyperplasia occurs in 15 per cent. of the female, but only 0·70 per cent. of the male pseudo-hermaphrodites, that is to say, it is twenty times commoner in the former than in the latter.[8] (b) The feminine pseudo-hermaphroditism was of an advanced type, as in 9 of them prostates were present, and 2 of these were described as completus. Now there are only two other cases of pseudo-hermaphroditismus femininus completus ; in one the adrenals are not mentioned (Mannec, 1833), and in one (Walcker (98)) they are described as normal. Hermaphroditism is not associated with hyperplasia or tumours of other glands, except the testicle, uterus, or ovaries. Thus Neugebauer (55) tabulated 50 cases, 45 being tumours of these organs, and the rest occurring in the oesophagus, liver, &c.

The evidence against the view that adrenal enlargement increases 'maleness' is: (a) The external genitals were described as precocious or fully developed in 4 children, viz. 1, 2, 4, and 10. (b) The occurrence of menstruation in 1 child, viz. Case 1, and the presence of mammae in one adult and two children. (c) The occurrence of obesity is perhaps more a female than a male characteristic.

[8] The recent case of ovary is included in these statistics.

(*d*) Meixner's (54) case of male pseudo-hermaphroditism; this is, however, a unique example. Moreover, both adrenals were of normal size, and the adrenal rests were very small, so that the net increase of adrenal tissue is less than in any of the female cases; besides, there is no evidence that the occurrence of the rests was not a coincidence. (*e*) If tumours of the adrenal cortex through their abnormal secretion can increase, as it were, the ' maleness ' of individuals, one would naturally expect the cortex to be relatively larger in males than females. Apparently this is not so. The weights of the whole adrenal given by several old observers in Vierordt (95) are about equal.

According to the recent observations of Scheel (77) the average weight in 92 males was 11·2 grammes and in 75 females 10·6 grammes, and there is no evidence that the proportion was relatively higher in males at puberty.

Grunner's (34) statistics are quite different. The average weight in grammes and the ratio of weight of the male to the female glands is as follows:—

	Male.	Female.	Ratio.
Under 4 years—	1·8	1·8	1
4–15 „	6·2	4·5	1·37
Adults	11	5·6	1·99
45–65 „	9·3	5·3	1·75

The value of these figures is vitiated by Grunner's failure to state whether the weights are based on the whole or a portion of the material obtained from 200 post-mortems.

Jackson's (118) statistics on the relative weights of various organs during prenatal development show that ' the suprarenal glands, unlike the kidney, are usually relatively larger in the female '.

The Occurrence of Female Sex Characters in Males.

As we have seen, there is much evidence to show that hyperplasia or malignant hypernephroma of the adrenal cortex in females is associated with a diminution of certain female and a development of certain male sex characters. The converse does not occur. Malignant adrenal hypernephromata in adult males are not very uncommon; Woolley gives 11 examples, the ages varying from 40 to 73. They are, I believe, never associated with the appearance of female sex characters, such as disappearance of hair from the face, the development of mammary glands, atrophy of the testes, or any other abnormal physiological change. Halban, however, alludes to some cases of gynaecomastia in adult males in whom the mammary enlargement was said to have followed orchitis from mumps.

Apart from pseudo-hermaphroditism, a congenital defect, the only occasion in which some male sex characters fail to develop is at times in acromegaly (to be referred to later) and after castration. If castration is performed before puberty, the beard fails to grow and the voice to crack, and some individuals become obese (Halban, Tandler, Gilford (115)).

Premature development of *female* sex characters in *females* is met with in certain ovarian tumours, as already mentioned by Clement Lucas, Parkes Weber, Brohl, Hoffacker (3 cases, referred to by Guthrie), Geinitz, Meurer, Reidel (referred to by Neurath), and Gaudier.

Premature development of *male* characters *in males* occurs not only with adrenal hypernephromata, certain tumours of the testicle, but also with growths of the pineal gland, as will be shown later.

The Relationship of the Pituitary Gland to the Adrenal Gland and Sex Characters.

As previously stated, the pituitary, like the adrenal, enlarges in pregnancy and after castration. But the relationship is even closer. Marenghi (53) discovered that extirpation of both adrenal glands is followed by hypertrophy of the anterior lobe of the pituitary, and Fischera (cited by Fischer) confirmed this. Landau, however, found adrenal extirpation without effect in rabbits (Hoskins (112)).

Fischer observed enormous hypertrophy of the adrenals, mainly cortical, in two cases of acromegaly. Delille (cited by Fischer) states that adrenal hypertrophy is frequent in acromegaly, and he was able by injecting pituitary extracts into animals to produce hypertrophy of the adrenal, especially the cortex.

Not only is there a functional connexion between the adrenal cortex and the anterior lobe of the pituitary, but in acromegaly, where the lesion is also in the anterior lobe, there may be disturbance of nutrition and sex characters which recall those obtaining in adrenal hypernephromata. Acromegaly is sometimes associated with 'dystrophia adiposo-genitalis', that is, with obesity and disturbances of sexual functions (Fischer (26)). There may be impotence or amenorrhoea, atrophy of the testes, ovaries, and uterus, with occasionally a prodromal increase of sexual activity. Sometimes the penis, clitoris, and labia are hypertrophied, sometimes infantile or normal. Creutzfeldt (cited by Fischer) found 'atrophia genitalis' in 36·4 per cent. and 'hyperplasia genitalis' in 2·5 per cent. of cases of acromegaly. Obesity is not so frequent as genital disturbances.

The influence of the pituitary will be understood by the following cases:—

Schlosser (cited by Eiselsberg) and Eiselsberg (23) have each described a case of acromegaly in a man with infantile genitals and complete absence of axillary and pubic hair, in whom, after the removal of a pituitary tumour, the hair grew and the sexual organs developed. Schlosser's patient was obese, and lost 1½ kilograms in weight after the operation.

Bychowski (15) published a case of acromegaly in a girl with infantile genital organs, a small amount of hair on the pubes and none in the axilla. Two months after a cyst of the hypophysis was drained she menstruated for the first time, but a second menstruation had not taken place eight months later. It is not stated whether the hair grew again.

Stumme (85) described a young woman who, for several years, menstruated irregularly with long intermissions. She was admitted with acromegaly. There

were small coarse hairs on the cheeks, and also a growth of hair along the linea alba. The voice was deep. A pituitary tumour the size of a hazel-nut was removed. Six months after the operation menstruation was regular every four weeks; hair on the face disappeared; the hands and feet became smaller. There is no note about the condition of the genital organs. Fischer, in his abstract, says the patient had a beard. This is, however, quite untrue. (See also Stumme's picture of her.)

Fischer explains dystrophia adiposo-genitalis by pressure of the enlarged anterior lobe of the pituitary upon the nervous substance of the *posterior* lobe and infundibulum.[9]

The Pineal Gland and Sex Characters.

Tumours in the pineal region, though rare, are occasionally, like those of the adrenal, associated with changes in sex characters, particularly true precocious sexual development. Neumann (121) has collected 22 cases of pineal tumour up to 1911; 19 in males, 3 in females, the majority in children. Ten are described as sarcomata, 3 as carcinomata, 3 as teratoma. Those with changes in sex characters are briefly summarized below:—

1. Ogle (123). Boy aged 6, pubic hair, greatly enlarged penis, testes normal size, tumour an alveolar sarcoma with haemorrhage; pituitary normal microscopically.

2. Oestrich and Slawyk (122), first demonstrated by Heubner. Boy aged 4, size of child of 8, pubic hair, enlarged testes and penis, mammary glands 2 cm. high, contained colostrum; tumour a psammo-sarcoma cysticum.

3. Gutzeit (quoted by Neumann). Boy aged 7, pubic hair, tumour cystic teratoma.

4. Frankl-Hochwart (quoted by Raymond and Claude). Boy aged 5, obese, looked two years older, pubic hair, enlarged penis and testes, erections, deep voice, tumour and teratoma containing neuroglia, pituitary normal.

5. Raymond and Claude (71). Boy aged 10, looked 13, obese, pubic hair, testes and penis abnormally small, tumour a vascular cystic glioma producing considerable pressure atrophy of the pituitary; adrenal contained nodular tumours, microscopical evidence of hyperactivity of cortex and medulla.

The genital atrophy in Raymond's case was due to destruction of the pituitary. The condition of the adrenals is noteworthy.

It is probably not a coincidence that these cases all occurred in male children, whereas adrenal hypernephromata are five times commoner in female.

The Cause of the Sex Abnormalities.

Is the adrenal hyperplasia, or neoplasia, the cause or effect of the changes in growth and sex characters, or are both secondary to a common cause? We have seen that renal hypernephromata are associated with changes in sex characters in 17 out of 18 children (Bruchanow's infant being the exception),

[9] On the other hand, the recent careful experiments on dogs and puppies by Crowe and Cushing (126) demonstrate that genital hypoplasia or infantilism, hypotrichosis, and adiposity follow partial removal of the *anterior* lobe.

and 6 out of 9 or 10 in young women, excluding Halban's and Alberti's cases. It is perfectly true that in the majority of instances hirsutes were noted first, but this is to be expected, as it was a striking feature and the tumour was deep-seated.   Thus in Goldschwend's (31) case, though the abdominal tumour and hirsutes were noticed simultaneously, the former must have preceded the latter.   The hair falling off the lady's face after Thornton removed the tumour, and the occurrence of the neoplasm in Orth's case during the second year of life, apparently long before the hirsutes, are strong evidence that the internal secretion of the adrenal tumour caused the abnormal growth.

Additional though indirect evidence supporting this view is afforded by two remarkable instances of precocious sexual development in children with a tumour of the ovary and testicle respectively, in whom the former childlike appearance returned after the removal of the tumour.

Clement Lucas, quoted by Guthrie, records the case of a girl, aged 7, who had menstruated several times.   The mammae were well developed, pubic hair present, and the child resembled a woman.   Lucas removed a solid tumour of the ovary most resembling a round-celled sarcoma with alveoli.   After the operation menstruation ceased, and the signs of puberty gradually disappeared. The tumour seems to have been of doubtful nature.   Dr. Goodhart said, ' Round-celled sarcoma seems the best name for it.'   It consisted of ' numerous alveoli containing 1–3 granular cells '.   It was probably not malignant.

Guthrie also quotes Sacchi, who described a boy aged $9\frac{1}{2}$ with very excessive development.   ' His right testicle was atrophied, the left was of enormous size. It was removed, and found to contain an epithelial growth.   The boy then became more childlike, and his beard fell out.'

Considering the great difference in the microscopical structure between many adrenal hypernephromata and the adrenal cortex, it is difficult at first sight to understand how such growths could produce sufficient internal secretion to cause such profound changes in metabolism.   It is well known that the tumour formation in general is associated with a diminution of the function of the cells concerned.   This, however, does not always occur; witness the secretion of bile by certain primary hepatic carcinomata, not only in the liver itself, but in the metastases.   Probably the degree of anaplasia is much less when the tumour first appears, and so the tumour cells are better able to manufacture more or less normal cortical internal secretion.

The view that hypernephromata directly or indirectly cause the sex changes is not negatived because they fail to occur in every case of typical tumour in young women, for the same lesions do not invariably produce the same effects in every individual; nor because they are usually absent in adrenal rests, and in ovarian and renal hypernephromata, for the former are too small to produce a physiological effect, and the latter rarely if ever arise from the adrenal cortex.   Neither is it negatived by the absence of marked sex changes in women after the menopause, for the sex characters have as it were become stereotyped through age.

Cortical enlargement and pseudo-hermaphroditism. The relation between cortical enlargement and pseudo-hermaphroditism seems to be rather different. It has been suggested that as the ovary and suprarenal cortex arise from the same *Anlage* the first may have received too large and the second too small a share; but this cannot be the explanation, as the ovaries were normal in Case 28. The almost invariable bilateral and hyperplasic nature of the adrenal lesions suggests that they are secondary or compensatory, as Marchand first believed. This view is supported by the enlargement which occurs after castration in the adrenal and in two other ductless glands, the pituitary and the thyroid, for in many of the cases of pseudo-hermaphroditism the ovaries had not functioned, as indicated in Table III.

Against this compensatory view the following facts may be urged :— In Fibiger's third case, that of an infant aged 6 weeks, the ovaries were normal microscopically, yet both the adrenals were the size of kidneys; again, in Engelhardt's case the adrenal lesion was unilateral. The single observation of Schenk and Soli upon the effect of castration suggests that if the adrenal lesion were compensatory, adrenal enlargement would be very common in male pseudo-hermaphrodites, as many have atrophied testicles, whereas it rarely if ever occurs.

It is unfortunate, however, that very few of the ovaries or testes in pseudo-hermaphroditism are examined microscopically. Yet fibrosis of the testicle must be common for this reason. Cryptorchidism is frequent in male pseudo-hermaphrodites (Neugebauer). It is well known that the sperm function of retained testicles is rarely developed and fibrosis ultimately occurs. Simmonds (82), the most recent writer on the subject of Fibrosis Testiculi, states that destruction of the gland tissue and fibrosis is of frequent occurrence in ectopic testicles. (See also Adami, Beattie and Dickson (8), and Quain's *Dictionary of Medicine* (68).) It is antecedently improbable that the adrenal lesion is the cause of the abnormal sex growth in Group I, and the effect of it, or some other cause, in Group II. It is much more likely that the essential factors concerned are the same in both cases, a supposition which is borne out by the occurrence of the intermediate types.

Development of adrenal cortex and sex organs. Could adrenal hyperplasia possibly cause the pseudo-hermaphroditism? The adrenal cortex first appeared very early, viz. in 8 mm. foetus, that is to say in the fourth week, and Wiesel found that in 12.5 mm., at the end of the fifth week, it already showed a delicate capsule and the character of the epithelial cells was more distinct, but there was absolutely no trace of the medulla (von Neusser). The first indication of distinguishing sex characters appeared at the third month; in the male the prostate and scrotum are developing in the fourth month, and the urogenital sinus persists in the female till the sixth month (Keith). Assuming, for the sake of argument, that hyperplasia of the adrenal cortex is the cause of certain cases of feminine pseudo-hermaphroditism, and the hyperplasia commenced in early foetal life, there would be plenty of time for it to exert its physiological

effect before the sex characters were fully established. Even if the adrenal hyperplasia did not either directly or indirectly cause the genital abnormalities of the pseudo-hermaphrodites, it was probably responsible for the male type of hair distribution which occurred in all the adult female pseudo-hermaphrodites.

Perhaps the full development of the symptoms found in adrenal hypernephromata may be due to associated derangement of other ductless glands, the pituitary for example. In acromegaly, obesity, amenorrhoea, uterine atrophy, and impotence may occur. Atrophy, however, of the external genitals with loss of pubic hair is much more frequent than hypertrophy; hirsutes is very rare. The only cases of malignant hypernephromata in which the pituitary has been examined are my own and Guthrie's; in both they were normal macroscopically and microscopically, and in Goldschwend's macroscopically. Still, sympathetic pituitary over-activity may be responsible for some of the effects previously attributed to the adrenal, such as clitoris hypertrophy. On the other hand, slight abnormal growth of hair in Stumme's case might equally be the result of over-activity of enlarged adrenals.

Further speculation is useless. It is certain that there is an intimate connexion between sex characters and the adrenal cortex. It is probable that adrenal hypernephromata either directly or indirectly cause the abnormal sex characters. It is possible that the bilateral adrenal hyperplasia also causes some of the lesions in pseudo-hermaphroditism.

Summary and Conclusions.

1. The adrenal cortex and medulla have a different development and different functions; the former is especially connected with growth and sex characters, the latter with blood pressure.

2. Tumours are rare, primary malignant tumours especially so, the most usual being (a) round-celled sarcoma; (b) adrenal hypernephroma; an epithelial-like growth of cortical origin.

3. Sarcomata are the commoner; they are more frequent in children, especially in male children. Adrenal hypernephromata are five times more frequent in female children, though in adults they are slightly commoner in males.

4. Sarcomata and adrenal hypernephromata differ histologically, and in children, at any rate, differ clinically.

5. Adrenal hypernephromata are associated with sex abnormalities, almost invariably in children, usually in adult females before the menopause, but apparently never in adult females after the menopause, or in adult males.

6. Adrenal rests or bilateral hyperplasia of the adrenal gland is found in at least 15 per cent. of female, but only 0·70 per cent. of male pseudo-hermaphrodites.

7. Hyperplasia and hypernephromata of the adrenal cortex in females are usually associated with a diminution of certain female and the development of certain male sex characters. The converse rarely occurs.

8. The only conditions in which some female sex characters are constantly

acquired in males, or male sex characters fail to develop, are after castration performed before puberty, and occasionally in acromegaly.

9. Premature development of female sex characters in females may occur with certain ovarian tumours, and of male sex characters in males with certain tumours of the pineal gland, adrenal cortex, and testicle.

10. In children and young adult females where the sex abnormalities are acquired there is usually unilateral malignant cortical neoplasia. The neoplasia probably directly or indirectly causes the abnormalities.

In pseudo-hermaphroditism the sex abnormalities are mainly congenital and the adrenal lesions, if any, are bilateral cortical hyperplasia or cortical rests. The hyperplasia possibly directly or indirectly causes the abnormalities, or some of them.

11. Rests from the adrenal cortex are common in certain localities, especially in infancy, except in the kidney. They are usually of minute size, and are not associated with sex abnormalities unless there is much enlargement, when such may sometimes occur in pseudo-hermaphrodites.

12. The enlargement of the adrenal cortex during breeding, pregnancy, and after castration, and the small size in deficient sexual development are additional evidences of the connexion of the cortex with sex characters.

13. The functional association of the adrenal with the pituitary and other ductless glands, and the appearance of certain sex abnormalities in acromegaly, indicate that a true solution of the connexion between the adrenal cortex and sex will only be found, when the inter-relationships of the various ductless glands are better understood.

14. Certain facts are opposed to the hypothesis that renal hypernephromata arise from the remnants of adrenal cortex, viz.—

(*a*) The great dissimilarity in microscopical structure between hypernephromata of the renal and adrenal glands.

(*b*) Renal hypernephromata apparently never influence growth or sex characters.

(*c*) The difficulty of explaining why adrenal rests, though comparatively rare in the kidney, should produce such a common tumour as the hypernephroma, by far the commonest renal tumour, while adrenal rests in other localities, though comparatively common, especially in early life, should, like the adrenal gland itself, so rarely produce tumours either benign or malignant. These considerations support the statements of Stoerk, Zehbe, and Wilson and Willis, who maintain that renal hypernephromata rarely if ever arise from adrenal rests.

15. Adrenal rests in the ovary are exceedingly uncommon. The ovarian hypernephroma does not produce the characteristic sex abnormalities; it probably arises from the lutein cells of the ovary itself.

I wish to thank Dr. Bulloch for three references, Mrs. Adams, Dr. French, Dr. Frew, and Dr. Ritchie for microscopical sections.

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DESCRIPTION OF FIGURES.

Figures illustrating the marked histological differences between four cases of adrenal sarcoma, adrenal bypernephroma, and renal hypernephroma respectively.

Adrenal hypernephromata in children with sex abnormalities. Figs.: 1, Ritchie's case; 2, Dun's case; 3, Adams's case; 4, French's case. × 300.

Note—Fig. 3 has been badly fixed; portions of Fig. 2 almost exactly resembled Fig. 3, but not shown in photograph; in Fig. 4 the perivascular arrangement is specially shown. (See text, pp. 170-1.)

Adrenal sarcomata in children without sex abnormalities. Figs.: 5, M. J.; 6, M. P.; 7, M. I.; 8, D. J. (Dr. Frew's cases.) × 300. (See text, pp. 159-173.)

Renal hypernephromata without sex abnormalities. Figs.: 9, M. S.; 10, T. M.; 11, D. T.; 12, M. W. × 300.

The 'small dark cells' are well seen in the middle of Fig. 10, and tubules with blood one half of Fig. 11. (See text, pp. 178-9.)
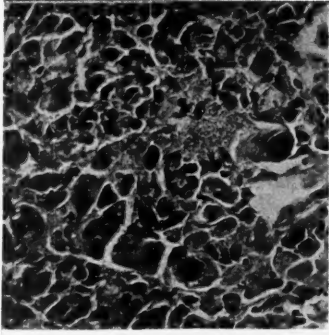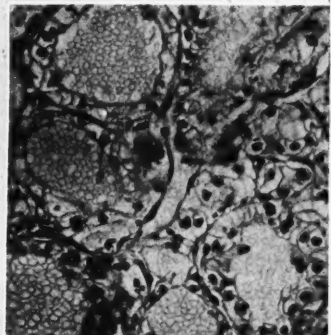
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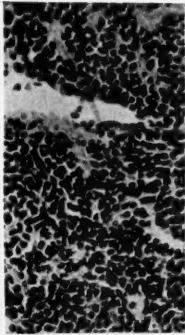
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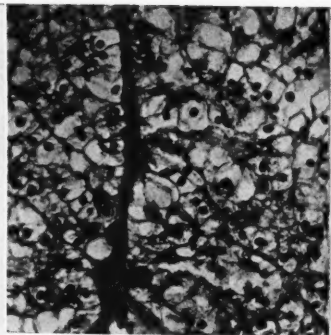
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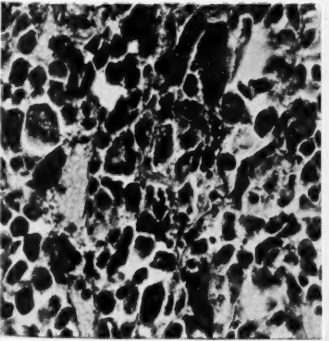
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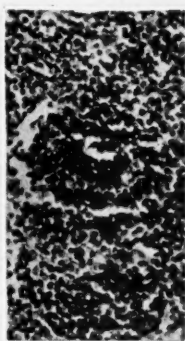
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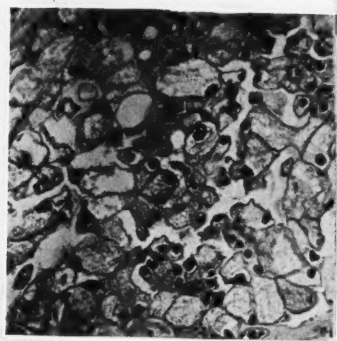
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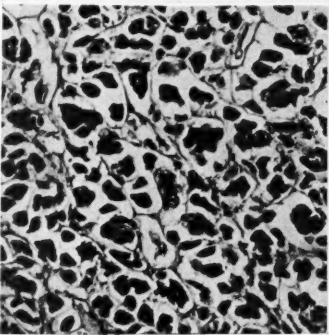
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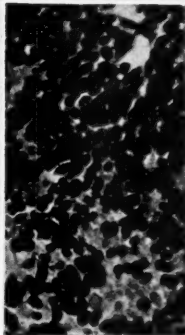
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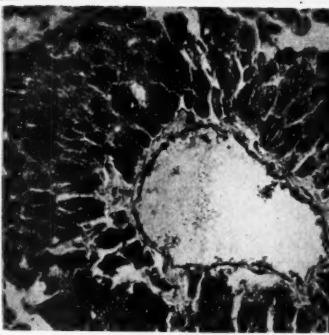
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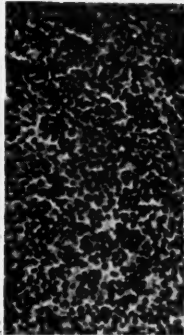
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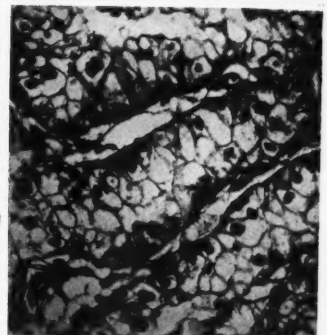
12

THE ANTIGEN (VACCINE) TREATMENT OF ENTERIC FEVER

By F. J. SADLER

CONTENTS.

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By international usage I am driven to call the injection of killed typhoid bacilli into typhoid fever patients by the name of vaccine treatment, though I consider the term 'vaccine', in this connexion, very inappropriate. I should prefer the term 'Antigen Treatment', for the object of the treatment is to produce such antibodies in the patient's system as will help him to deal with the infection from which he is suffering, a use to which vaccine proper is never put.

The first account that I can find of the vaccine treatment of typhoid fever patients is by E. Fraenkel in 1893 (7). He used typhoid bacilli sterilized by a temperature of 63° centigrade. With these he made a vaccine of such strength that 3 cubic centimetres injected in the peritoneal sac of a guinea-pig weighing 350 grammes produced no symptoms. Fraenkel started with half a cubic centimetre of such vaccine, followed by one cubic centimetre the next day, and any subsequent increase of the temperature was treated by injecting 2 cubic centimetres more. He had fifty-seven cases—twelve of which were bad cases, and the rest medium—and found that in the majority of his cases there was a definite improvement of temperature by the fourth or fifth day. He does not print the temperature charts nor does he give the case fatality.

In 1901 Chantemesse began to treat typhoid cases with his anti-typhoid serum, using a method of dosage that suggests a vaccine treatment rather than a serum treatment. This, of course, is not my criticism, but Wright's. Further, Chantemesse, in a paper read at Berlin (3) in 1907, states that in his patients

in the first three or four days after an injection the opsonic index rises rapidly. This rapid rise of the opsonic index corresponds with the rise after the injection of vaccine noted by all those users of vaccine who have determined the opsonic indices of their patients. Chantemesse also thinks that during those first three or four days there must be an intense destruction of bacilli, which throws into the circulation of the patient, already poisoned by typhoid fever, fresh poisonous products of the killed bacilli, and that in consequence of this increase of poisoning the patient reacts by having a feverish period which he calls the ' period of reaction '.

Chantemesse also gives a larger or smaller dose of serum, in inverse proportion to the gravity of the case; and speaks of the dose for a bad case as being four or five drops, a dosage which again suggests vaccine rather than serum treatment. But whatever the explanation of the action of the serum there is no doubt at all about Chantemesse's wonderful results. His case fatality in cases treated with serum is 4 per cent., compared with a 17 per cent. case fatality among all the other cases of typhoid fever treated in Paris hospitals. I also understand that when Chantemesse experimentally ceased using his serum for a short period his case fatality at once jumped up again to the level of that of the rest of Paris. The problem, therefore, before the users of vaccine is to get an equally good case fatality by the use of killed typhoid bacilli.

Birt (2) suggested ten million killed bacilli as an initial dose, but does not seem to have actually treated cases with vaccine. Semple (13), in the *Lancet* of June 12, 1909, reports nine cases treated with vaccine, and says that auto-genous vaccines gave better results than stock vaccines. Beginning with six millions as an initial dose, in subsequent cases he increased this dose to thirty or even forty millions, and recommends autogenous vaccine in doses of fifteen to thirty millions on four to six consecutive days, and as early as possible in the disease. Smallman (14) had thirty-six cases with three deaths. The initial dose recommended by him is 300 to 350 millions, repeated five or six days later. Two of the three deaths were in fulminant cases, the patients dying about seven days after admission to hospital and after one injection of vaccine only. In the charts published by Smallman the dosage varies from 144 millions to 356 millions, 200 to 300 millions being the most frequent. Leishman approves of this and considers that nothing under 300 millions is of any use.

In America Watters and Eaton (16 and 17) publish thirty-four cases with two deaths (in the *Boston Medical and Surgical Journal* of April 22, 1909, page 508, and the *Medical Record* of January 6, 1909, page 93). Their initial dose varies from fifteen to fifty millions with an interval of four or five days. They are in favour of larger doses. Sappington (12), in the *Journal of Medical Research*, June, 1910, publishes twenty-two cases of enteric fever. He began with ten- to fifty-million doses, and later found smaller doses of five to thirty millions more satisfactory. He remarks that vaccines vary in strength, and advises that it is best to begin with a small safe dose and increase if necessary.

He adds that the interval is more important than the amount, and is perhaps the key to successful treatment. Sappington advises that a start should be made with five to ten million bacilli, followed on the succeeding or second day according to reaction by a second dose of twenty-five millions. He finds that the local reaction is severe in non-typhoid cases only. W. M. Richardson (11) in the *American Journal of Medical Science*, 1908, says that, to be successful, inoculation treatment in typhoid fever must begin very early, and considers that the slower the pulse rate the greater the chance of brilliant results from the vaccine, and further that an improved pulse is more important than a lower temperature. He seems to use daily inoculations of 25–30 million bacilli. All these observers are agreed that vaccine treatment is of great promise, and perhaps the most extraordinary thing is that with such varying doses they should all have obtained satisfactory results.

I have tried to arrive at some explanation of why one school of thought arrives at the conclusion that nothing under 300 millions of typhoid bacilli is any use, while another school advises very much smaller doses, and on this point I think two protocols in Ehrlich's (4) *Studies on Immunity* are particularly suggestive.

TABLE I.

Inactive Dysentery Serum. c.c.	Active Horse Serum. c.c.	Dysentery Culture.	A. No. of Colonies on the Plate.	B. Growth in the Tubes.
0·01	0·3	1·0 c.c. (1/500 mg.)	∞	+
0·0075	0·3	,,	∞	+
0·005	0·3	,,	∞	+
0·0025	0·3	,,	almost 0	–
0·001	0·3	,,	0	–
0·00075	0·3	,,	almost 0	–
0·0005	0·3	,,	about 50	–
0·00025	0·3	,,	,, 100	+
0·0001	0·3	,,	,, 1000	+
0·000075	0·3	,,	several thousand	+
0·00005	0·3	,,	∞	+
Control { –	0·3	1·0 c.c. (1/500 mg.)	several thousand	+
–	–	,,	∞	+
0·1	–	—	0	–
–	0·3	—	0	–

TABLE II.

Inactive Dysentery Serum. c.c.	Active Human Serum. c.c.	Dysentery Culture.	No. of Colonies on the Plate.
0·01	0·3	1·0 c.c. (1/500 mg.)	∞
0·003	0·3	,,	∞
0·001	0·3	,,	∞
0·0003	0·3	,,	few
0·0001	0·3	,,	0
0·00003	0·3	,,	about 100
0·00001	0·3	,,	,, 1000
Control { –	0·3	1·0 c.c. (1/500 mg.)	∞
–	–	,,	∞
0·1	–	—	0
–	0·3	—	0

These two tables are both concerned with the observed results of mixing in a test-tube varying amounts of inactive dysentery serum, and constant amounts of complementing serum, and dysentery culture, incubating the mixture at 37° centigrade for three hours and then inoculating agar plates with six drops of the mixture. The 'inactive dysentery serum' is the serum from a horse highly immunized against the dysentery bacillus. The serum by heating is rendered inactive (or unable by itself to destroy living dysentery bacillus). In Ehrlich's terminology it then contains amboceptors only, which require the addition of complement to enable them to destroy bacilli. But this only happens when a certain amount of inactive dysentery serum is used. If more than this critical amount, or less, is taken the dysentery bacilli are not killed, or not *all* killed, and growth on the agar plates results. When the very *small amounts* of inactive serum are used the obvious explanation is that not enough bacteriolysin is formed to kill all the bacilli. When the amount of inactive serum is too large the failure to kill is explained hypothetically by deflexion of complement. That is to say, there is such an excess of amboceptors that part of them attach themselves to all the complement available, and the other part attach themselves to all the bacilli available, and there is no complement left for the latter set and no bacilli left for the former set, wherefore no destruction of bacilli can occur. From the two tables it is seen that the phenomenon of deflexion of complement occurs whether the complementing serum is from a horse or human. The same phenomenon has been shown to occur also in the case of vibrio metchnikov (5) and vibrio nordhafen (6).

I suggest as a possibility that, just as in Table II the result of using 0·0003 c.c. of inactive serum and 0·00003 c.c. of inactive serum is about the same, while the intermediate quantity 0·0001 produces the complete bactericidal effect, so also the use of large quantities of vaccine leads to deflexion of complement in the human body, and leaves a comparatively small active balance of antibodies, while the small doses produce *no* deflexion of complement and therefore act in proportion to the amount injected, whereas intermediate doses may be dangerous to the patient through a too complete bactericidal action.

Passing to the method by which injection of killed typhoid bacilli may be supposed to assist a patient to overcome his infecting organisms the two following observations seem to be established. Leishman, Harrison, Smallman, and Tulloch (9) in a study of the effects of prophylactic typhoid inoculation demonstrated the development of various immune bodies with the exception of opsonins, and further there seems to be a general concurrence of opinion that typhoid immunity is attained from bacteriolysins and other antibodies rather than opsonins.

In typhoid fever patients treated by vaccine injections all observers who have taken the opsonic indices agree that (1) the opsonic index is already raised above normal by the seventh day of the disease, and (2) that the result of injecting vaccine is still further to raise the opsonic index, at all events for a short time ; (3) that with the beginning of convalescence the opsonic index falls

to normal or below normal.   On the other hand, Andrewes (1), in his second Croonian Lecture of 1910 (*Lancet*, July 2, 1910), shows that the result of injecting 200 million killed typhoid bacilli into a rabbit is to produce a diminution of the polynuclear leucocytes and of the lymphocytes circulating in the blood ; that this is followed by a polynuclear cytosis at the end of three hours and a lymphocytosis at the end of six hours.   The polynuclears are the 'microphages' of Metchnikoff and are assisted in their work of phagocytosis by the opsonins.   I throw out the suggestion that the lymphocytes may be concerned in the production of bacteriolysins, and that in any case differential blood-counts carried out on typhoid patients under vaccine treatment might give useful results.   It is probable, therefore, that both the bacteria-destroying antibodies and the opsonins are factors to be considered in the vaccine treatment of typhoid fever.   Chantemesse thinks that a great destruction of bacteria is the result of injecting his serum and that the endotoxins so liberated cause the feverish reaction following the injection.   If A. E. Wright's opinion that the serum really acts as a vaccine is correct, it follows that in vaccine treatment the same precautions should be taken to diminish the initial dose in proportion to the severity of the case as in the serum treatment, lest the antibodies produced by the vaccine liberate more endotoxins than the patient's nervous system can deal with.   Possibly also the local formation of antibodies enables the polynuclears and lymphocytes to deal more actively with the invading bacilli, and so turns the fortunes of the war in favour of the defending cells or body fluids.

To come to my own work, at first I was impressed by two things : (1) the established practice of immunizing healthy people against typhoid fever by injecting 300 million bacilli as a first dose and then following this up *ten days* later by a much larger dose ; (2) by Chantemesse's results with very minute doses (five drops) of antityphoid serum and my conception of the comparatively small amount of vaccine likely to be present in such a dose if A. E. Wright was correct in believing that the serum produced a vaccine action. I therefore fixed on two millions of killed bacilli as a suitable initial dose and ten days for the space between doses.   A further advantage of such a minute initial dose seemed to be that I should at least do no harm.   Among my early cases there was a sufficient number showing definite clinical improvement five days after a dose of two millions to encourage me to persevere.   This improvement is marked by a fall of temperature and by a return of appetite to the patient.   In fact, one of the difficulties which result from the treatment is the hunger of patients with haemorrhage from the bowel, even though the patient's tongue may still present the dirty glazed appearance so common in severe cases of typhoid.

Two early cases showed me that increasing the dose of antigen was inadvisable.   The idea was to follow the regular practice in immunizing healthy people against typhoid fever, and in these two cases I gave four millions as a second dose.   Subsequently I found it much better to follow Chantemesse's plan and give half the initial dose as a second dose.   The diminution of the

dose accords also with A. E. Wright's observation (18) that ' if after an excessive dose of antigen the bacteriotropic pressure remains below normal, it can (after constitutional symptoms have passed away) be restored by injecting a minimal dose of antigen '.

It was only after the publication of Dr. Andrewes' Croonian Lectures on ' The Lymphocytes in Infection and Immunity' and a conversation with Dr. Andrewes that I realized that by the tenth day after the first injection the condition of oversensitiveness to the antigen might have begun, so I then started to re-inject as soon as the improvement after the first injection began to pass off, and this soon brought me to my present practice of reinjecting on the fourth or fifth day, and every subsequent fourth or fifth day till convalescence is established.   As there is some difficulty in getting particularly virulent typhoid bacilli (except in my first few cases when I used a vaccine made from bacilli specially supplied for immunization against typhoid fever), I have used vaccine prepared by Dr. Henry from the Stock Cultures of Sheffield University, which are virulent enough to work satisfactorily in Widal's reaction.

For the purpose of starting treatment on modern lines 1910 was unfortunately a very bad year; for only fifty-five cases of typhoid fever were isolated at the Kendray Hospital instead of the usual 100 or more, and of the fifty-five only fifty-two were treated with vaccine. I have counted no case as typhoid unless typical rose spots and enlargement of the spleen were observed independently by my partner, Dr. Fryer, and by myself, unless Widal's reaction was positive. There are two or three exceptions to this rule, but as all these exceptions died, their inclusion is adverse, and not favourable, to my statistics.

Review of Cases.

To give a general idea of the effects of vaccine treatment I first illustrate contrasted cases, of varying degrees of severity, viz. 1909 cases not treated with antigen and 1910 cases treated with killed typhoid bacilli.
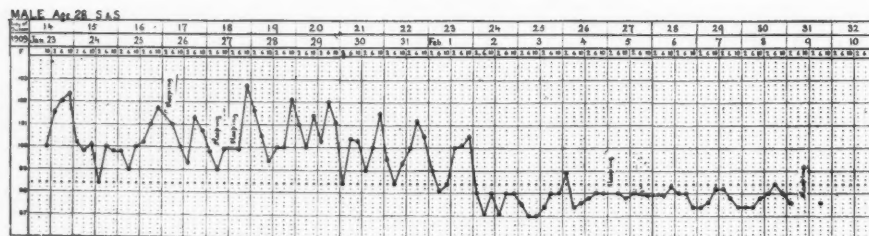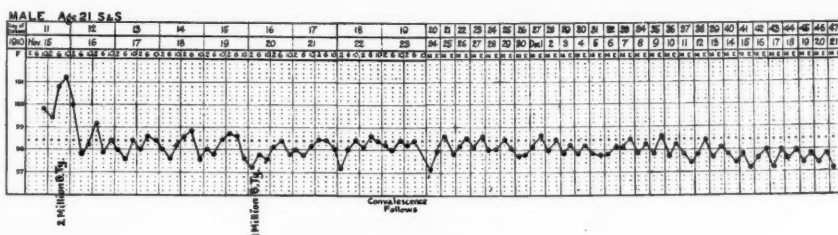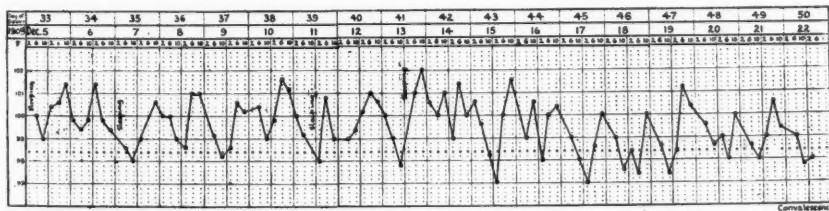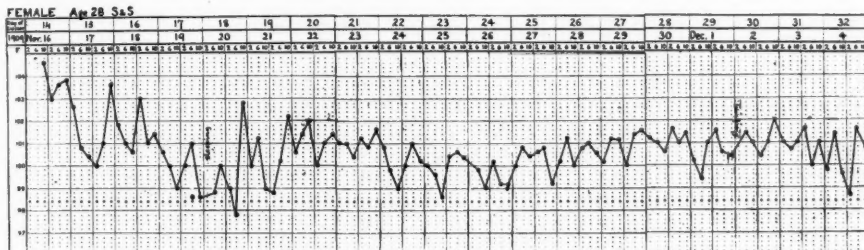

Case I.

Case I. Walter S., aged 28 years.   This was a very mild case of 1909 ; the man was admitted on the fourteenth day of the disease, and the temperature, after running the usual remittent and finally intermittent course, fell to normal

on the twenty-fourth day, from which point convalescence set in.   Dr. Houlton, who served in South Africa, tells me that the twenty-one day case of typhoid was very common in South Africa, but at the Kendray Hospital these cases were so rare that I used to consider them curiosities except in children.   Possibly the mildest cases are nursed at home and so have not come under my observation.

  Case II. Harry A., aged 21.   This was a 1910 mild case treated with vaccine after the method of dosage and spacing of doses that I have finally adopted. The case was admitted with rose spots and enlarged spleen on the eleventh day

Case II.

Case III.

of the disease.   He got two million killed typhoid bacilli injected on admission. Two days later the temperature had fallen to normal, and to make certain on the sixteenth day one million more killed typhoid bacilli were injected and his convalescence continued uninterruptedly.   I have had four other precisely similar cases in 1910, and many others who, with one injection only, became convalescent within ten days of the first and only injection (see appendix).

  Case III. Florence C., aged 28.   This, a 1909 case of medium severity, was, from a hospital point of view, a far more common type, which recovers

without giving rise to any very great anxiety though running a long course. The patient was admitted at the fourteenth day, and on the fifteenth day had a small haemorrhage, which recurred on the eighteenth day. The temperature kept on its usual remittent course till the thirty-second day, when, for the first time, it took on a more intermittent type. Convalescence did not begin till the fifty-first day.
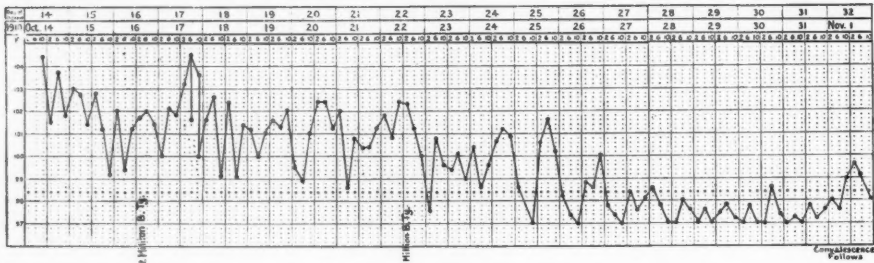

Case IV.

Case IV. Mary O, aged 17. This corresponding case of 1910 was moderately severe and was admitted on the fourteenth day. She was not injected till the sixteenth day, for it chanced for the moment no vaccine was available. Five days later, on the twenty-first day, the temperature had fallen to a lower level, only to rise again the next day, when a second injection was given. Five days later than this the patient was convalescent, the temperature remaining subnormal, except for one little rise on the thirty-second day.
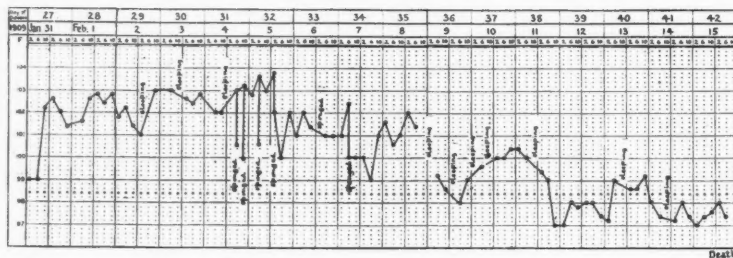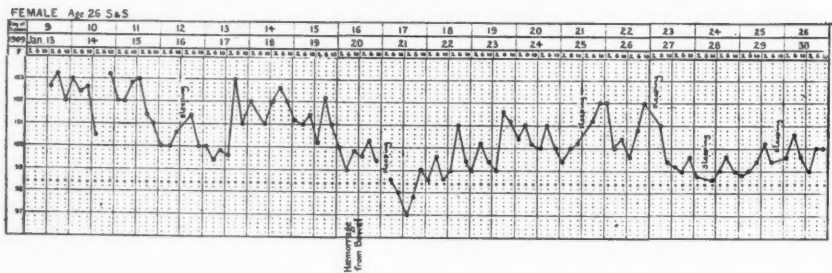
Case V.

Case V. Esther B., aged 26. This was a moderately severe case of 1909 which ended fatally. The patient was admitted on the ninth day. At the

thirteenth day, or about the end of the first fortnight, there was a characteristic fall of the temperature almost to normal. On the sixteenth day there was haemorrhage with a fall of the temperature to normal, followed by a subsequent rise, the temperature continuing at a varying level, but never quite down to normal. On the thirty-first day there was a sudden turn for the worse, the temperature jumping up to 102°; this in two days was followed by a serious weakening of the heart. On the thirty-sixth day the temperature fell to about normal, but though the temperature remained low, on the fortieth day she had distension of the abdomen, on the forty-second day several rigors, followed by death. This was a moderately severe case, where all seemed to go well up to the twenty-seventh day and matters again seemed to be improving on the thirty-sixth day, but the patient, being severely poisoned, collapsed and died. Vaccine treatment would probably have saved this patient.
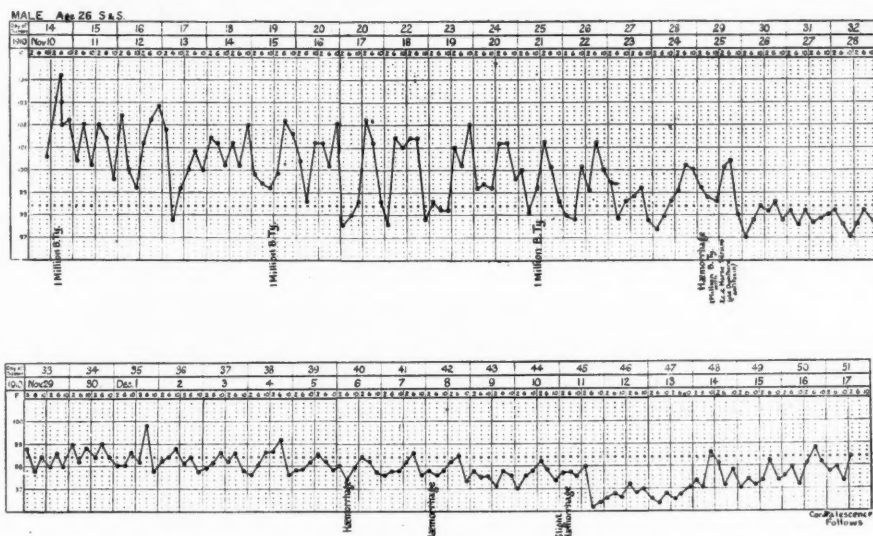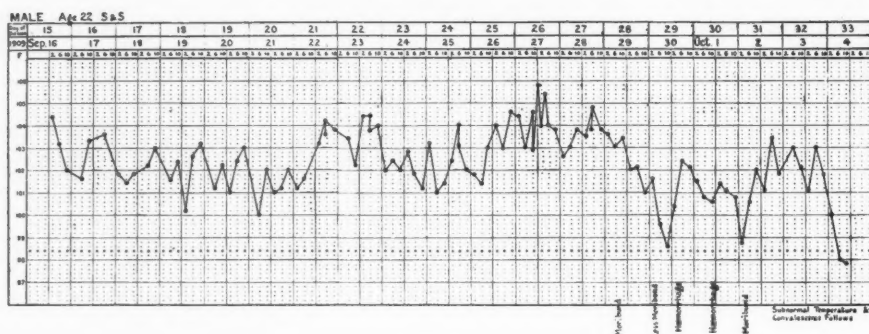

Case VI.

Case VI. John K., aged 26. This was a severe 1910 case with haemorrhage. He was admitted on the fourteenth day, and got two million typhoid bacilli on admission. Five days later his temperature was at a decidedly lower level, and another million bacilli were injected. On the twenty-fifth day, the temperature being then remittent in type, a further injection was given, and four days after that another million with one cubic centimetre of horse-serum in the form of diphtheria antitoxin was injected. From this point the temperature became normal and remained practically normal on into convalescence, but for all that he was really still very seriously ill.

On the twenty-ninth day the horse-serum was injected because of haemorrhage in the stool, and there was no further haemorrhage till the fortieth day. The haemorrhage recurred on the forty-second and forty-fifth days, and it was not till the fifty-first day that his real convalescence began.

This case illustrates one of the difficulties which result from the vaccine treatment. When the patient's temperature begins to be normal, as a rule he is also desperately hungry, and this case in particular, all through this haemorrhage

from the bowel, was extremely hungry, and yet I dared not feed him for fear of perforation, which is one of the complications which seems not to be avoided by vaccine treatment.

Case VII. Fred M., aged 22. Another of the 1909 cases was a very severe case with haemorrhage. So severe was the disease that on two occasions I wrote him down as moribund, and after the second of these occasions I have reason to believe that the man's coffin was ordered. Forty-eight hours later the man began to convalesce.
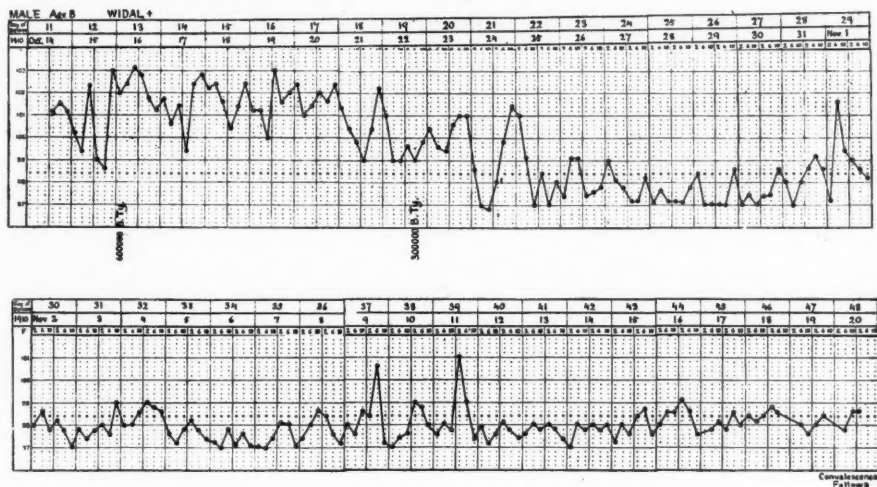

Case VII.

I describe both these severe cases from 1909 because they illustrate the great uncertainty in the past about the conclusion of an attack of typhoid fever. A patient that seemed to be doing well would quite suddenly get worse and die. A patient, on the other hand, that seemed to be absolutely hopeless, I am thankful to say did occasionally recover.

Case VIII. Stanley T., aged 8. This, a corresponding case from 1910, showed the fall of temperature to sub-normal level within five days of the second injection, though the patient was decidedly ill for a considerable time after this. It illustrates also the necessity of giving a smaller dose than usual in a bad case. I selected 600,000 bacilli instead of a million, which is what I should give to an ordinary case at the age of eight years, on account of the severity of the child's symptoms on its admission. The first dose controls the amount of the second, and a further 300,000 bacilli were injected on the nineteenth day, but these two doses were sufficient to bring the temperature down to normal.

On the nineteenth day, when his temperature appeared to be improving greatly, he was noted to have a meningeal cry and moaning, retraction of the head, and internal squint of the right eye. On the twenty-fifth day, when his temperature was already of a convalescent type, he began to have difficulty in swallowing. On the twenty-eighth day it was necessary to feed him entirely through the nose, the patient being unable to swallow, and being at the same time quite unconscious. The nasal feeding continued necessary till the sixty-first day, though about the forty-ninth day he was able to swallow a little water. On the fifty-first day he was thought to have recognized his friends, and on the sixty-first day he certainly recognized the tray of instruments for lumbar puncture and made continual outcry until the tray was removed. On this day he had the first food by the mouth since he lost the power of swallowing. Two days later he spoke his first words since admission, and after that his convalescence was steady, though there was a curious cataleptic rigidity of the muscles common in

the insane, but the solitary case in more than a thousand cases of typhoid that I chance to have treated in the Kendray Hospital. This cataleptic rigidity began to improve rather rapidly about the hundred and tenth day.

Case VIII.

Case IX. John C., aged 26. So much for the contrast between the old type of case and the vaccine-treated type. Before I relate my mistakes and the lessons I have learnt therefrom, I present a case with relapse, in which the injection of a million killed bacilli brought the original attack to a rapid conclusion within five days, and a further injection of half a million bacilli on the fourth day of relapse brought the relapse to an end within another five days. On the day following the last there was a fine crop of rose spots. From the next day convalescence was completely established. This is a case which encouraged me to persevere with the vaccine treatment.
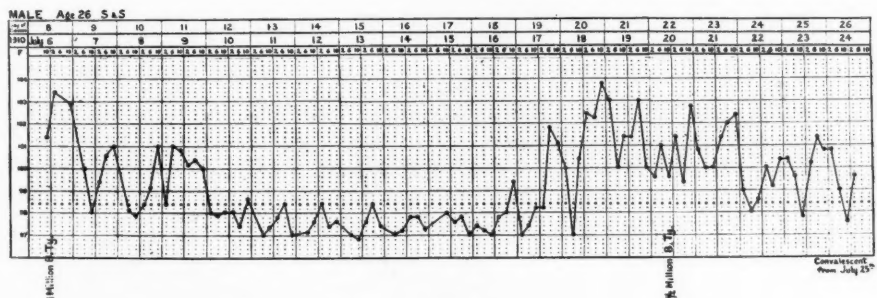

Case IX.

Case X. Dorothea L., aged 4. This, the first of the mistakes, is instructive. It chanced to be a cross-infection ; the child, suffering from scarlet fever, took typhoid fever while in the Scarlet Fever Ward. On the tenth day of the typhoid

fever half a million killed bacilli were injected, the child being only four years old, and having an enlarged spleen and large crop of rose spots. Four days later the child was distinctly better and crying out less from pain. It is at this point that I ought to have injected 250,000 more bacilli. As it was one of my first cases of injection I may perhaps be excused for not realizing this and for hoping, as I did, that the child would continue to improve.
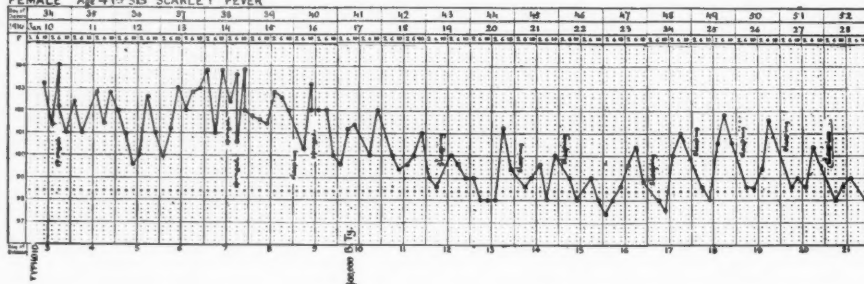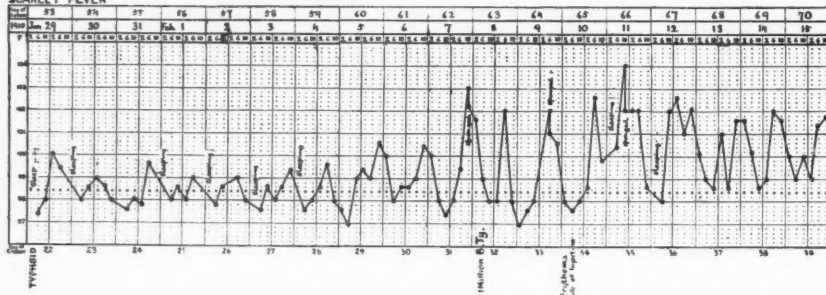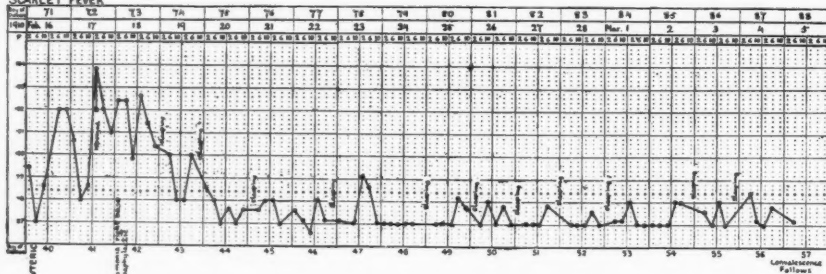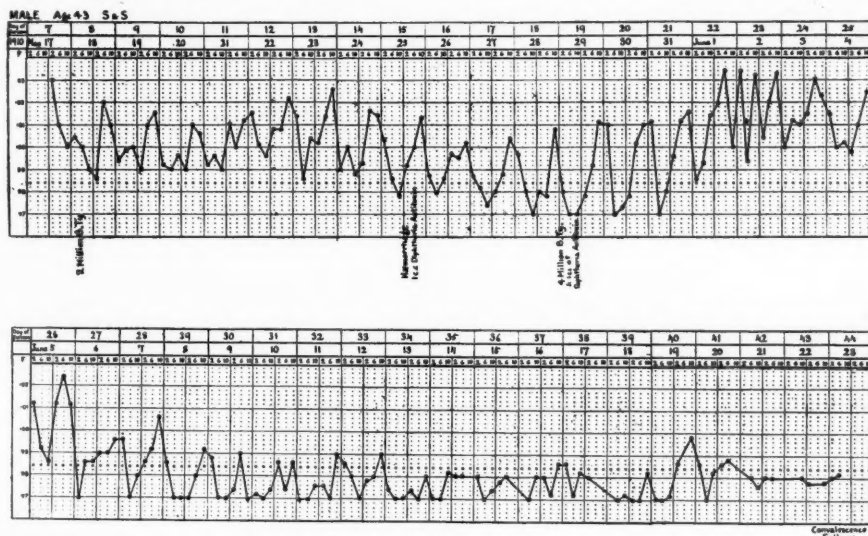

Case X.

However, about the sixteenth day the temperature began to rise again and the child definitely became worse. I was at this time influenced in my views of the method of vaccination by the interval recommended in the immunization of healthy people against enteric fever, when you are instructed to give 300 millions for the first dose, and ten days later a very much larger dose. Therefore I marked the tenth day after injection as a possible day for repetition, but in consideration of a not very serious amount of fever decided to leave her alone.

For the next ten days the temperature continued of a typhoid fever type, but just over and under normal. Finally, on the thirty-second day, the temperature having risen to 103° the night before, and fallen to 98° at the time of my visit, I decided to inject one million killed bacilli and thereby made a double mistake. In the first place I increased instead of diminished the dose, and in the second place the interval since the last injection was far too great. What followed was that the child had an attack of pneumonia, with a temperature of somewhat irregular type, but with the temperature falling from over 102° to 97° within thirty-six hours, i. e. by crisis, after which the child became convalescent. In this case there was a little erythema at the site of the second injection two days after it was given, a quite exceptional reaction with my dosage.

On looking back on my experience I cannot be certain that that attack was not anaphylactic in character. At all events that is a possible explanation.

Case XI.

Case XI. Arthur T., aged 43. This shows me still under the influence of the increasing dose theory, and of the bad results of such increase. This patient was terribly afraid that he was going to die, and being admitted on the seventh day had two million typhoid bacilli injected on the eighth day of the disease. Four days later, though there was no very great improvement in the temperature, the man was decidedly hungry. Three days later he had haemorrhage and was treated with a cubic centimetre of diphtheria antitoxin. On the nineteenth day, there being some improvement in the temperature, I injected four million bacilli together with another cubic centimetre of diphtheria antitoxin, on account of a further slight haemorrhage. For the next week this patient was very ill indeed; I was extremely anxious about him, and I have very little doubt that the increase of the severity of the symptoms was due to anaphylaxis, although there was no evidence of pneumonia. On the thirtieth day, having got well over his anaphylaxis, he rapidly became convalescent. These cases show the double mistake of waiting too long for the second dose of vaccine, and of giving it in increasing instead of diminishing doses.

Case XII. Alfred M., aged 29. I now have to deal with the cases which died. The first case was admitted on the twentieth day with a temperature so nearly normal that I did not for a few days think it worth while to give him any vaccine, but on the twenty-sixth day, the temperature having become slightly more irregular, I gave him two millions, with the result that two days later he began to complain bitterly of hunger. From the twenty-sixth to the fortieth day the temperature ran an uninteresting course, never remaining permanently normal nor yet rising much above the normal line.
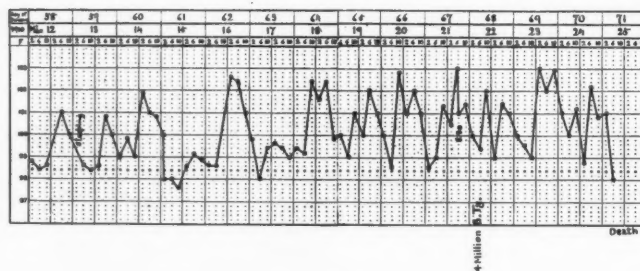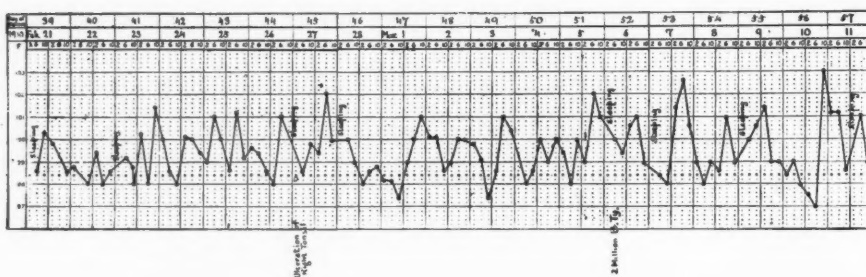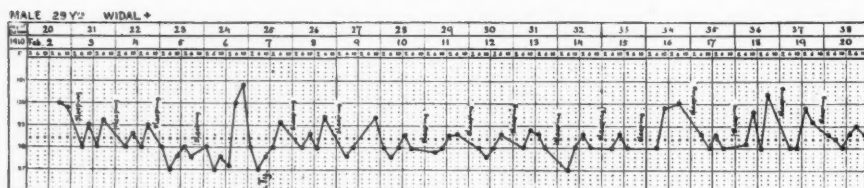
Case XII.

On the forty-first day, or three weeks after admission, the temperature began to assume a more irregular type, and with a distinct increase of the fever. On the forty-fifth day he complained of sore throat, and there was found to be ulceration of the right tonsil. The ulcer was very deep, and was suspected of being syphilitic. It began to improve between the fiftieth and fifty-second day with biniodide of mercury treatment in addition to local treatment with chlorine. At this point, with the evidence of throat improvement, I thought it

worth while to give the patient another two millions of the vaccine. The following day there seemed to be a negative reaction, followed by an improvement in the temperature during the three next days, and the patient said he felt better. On the sixtieth day the ulcer looked much cleaner, but the temperature persisted in its fluctuations. On the sixty-eighth day, as the improvement of the throat was at a standstill, and there was some cough, I injected four millions of typhoid bacilli. Two days later there was unmistakable pneumonia, and the following day the patient died. At the time I regarded this as a septic pneumonia, secondary to the ulcerated throat, and still think that is a possible explanation; but taken in conjunction with the deterioration of the other case (Case XI, *supra*)—to whom I also gave four million killed typhoid bacilli— and the considerable length of time that elapsed between the injections, it is just possible that this patient had become over-sensitive to the vaccine.

Case XIII. Elizabeth W., aged 25. On admission she was suffering from muttering delirium, having begun only a week before with severe pains in the head, and being a very severe case of typhoid of a cerebral type. The first two days after the injection there was an increased rise of temperature as if there had been a negative phase, which was followed by an apparent improvement in the next three days. On the day before the death I noted that the patient was
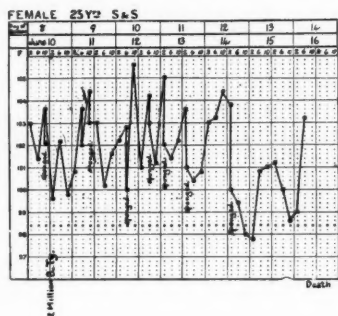

Case XIII.
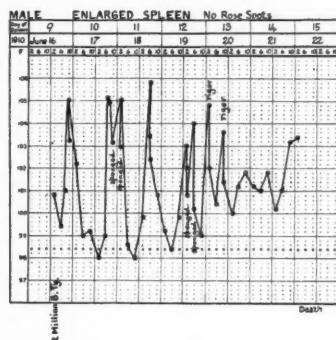
Case XIV.

taking better but that the lips and face were a little dusky, and I felt somewhat doubtful whether the sudden fall of temperature was due to haemorrhage or the end of the second week or to the vaccine. However, during the following night the patient died from heart failure, poisoned, I believe, by the toxins of the disease. As a result of this case I decided that in equally bad cases I would give half a dose of vaccine to start with, that is to say, one million killed bacilli.

Case XIV. James C. On the same day of the month as the previous patient died, the next case that died was admitted, and was given two millions of bacilli by my partner, Dr. Fryer, before I had the opportunity of discussing the matter with him. This man may, or may not, have had typhoid. His spleen was enlarged, but there were no rose spots, and I regret very much that I did not have his blood tested for Widal's reaction. He had begun nine days before admission with a shivering attack. He had green liquid stools and there was a discharge from his left ear. After admission he had a rigor and twitching of the right side of the body. Between the rigors the temperature fell to normal.

On the twelfth and thirteenth days he had four rigors. There was some consolidation of the upper lobes of the right lung with coarse râles on the thirteenth day. On the following day there was a marked pleuritic rub on the left side of the chest at the base in front, and in the night he died, just five days after the injection of the vaccine. I have some doubts whether this man really had typhoid, but I accept him as such because he emphasizes the importance of the previous case, and of the principle enunciated by Chantemesse as to giving a smaller dose in bad cases.

Case XV. Florrie H., aged 22. I here interpolate a fatal case which presents some features which I confess I do not yet understand nor am quite able to account for. She came in on the fifth day of the disease, had no rose spots or enlargement of the spleen on admission, but both these subsequently
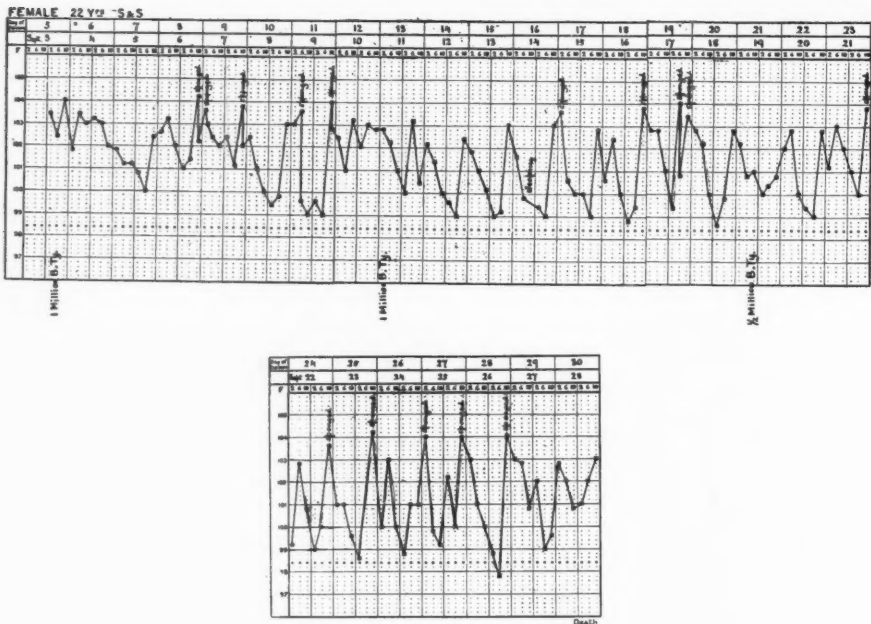
Case XV.

appeared. She received one million bacilli on admission and a further dose of one million eight days later, and half a million bacilli eight days after that, but none of these injections produced any satisfactory improvement in the temperature. After the third injection her heart began to get weaker and weaker till she died of heart failure on the thirtieth day of her illness. I think that possibly an earlier injection of perhaps half a million on the tenth day of the disease might have influenced the subsequent course of illness more favourably. Three days after the second injection the urine began to be passed more freely and the patient seemed a little brighter. On the eighteenth day it was noted that there was from time to time an offensive vaginal discharge. It is possible that this case belongs to a comparatively rare class of patients who are not helped by vaccine treatment, such cases seeming to crop up in all the other diseases which are treated by vaccine habitually.

The next two cases show, I think, that not much is to be hoped from vaccine treatment at a late stage of the disease.

Case XVI. Harry K., aged 19, had been an ambulatory case to start with, and the disease had reached its twenty-eighth day when he was admitted. He received two million typhoid bacilli on admission as he did not seem desperately ill, and it is somewhat interesting to note he was exceptionally tender at the site of injection the following day. He had subsequent nose-bleeding, and within five days of the injection died from failure of the heart.

Case XVII. Richard B., aged 34, was admitted about the fortieth day of the disease. He too had been an ambulatory case, and had been going about consulting various doctors to within four days of his admission. He had
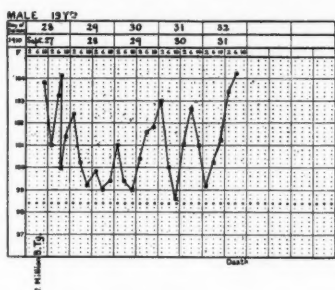
Case XVI.
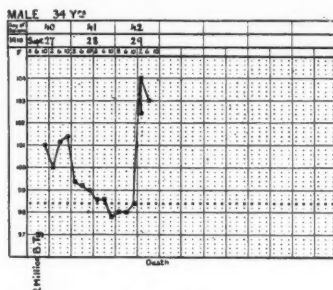
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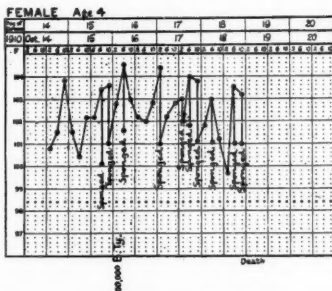
Case XVIII.

had 'consumption of the bowels' when an infant, and there was some evidence of tuberculous changes of the left apex. He had two million bacilli injected on admission, as, though in a low condition, he did not seem gravely poisoned by typhoid fever. However, on the following day there were constant movements of the mouth, culminating in violent delirium in the night. The delirium continued and he died on the second day after his admission. Besides the 'consumption of the bowels' as an infant, he had had rheumatic fever at the age of seven years and 'low fever' at the age of thirteen, when he was ill about fourteen weeks. He had never been very strong. In this case—as in the last—I think it possible that the injection of vaccine was too late to be of use, and the dose possibly too large for the stage the disease had reached.

Case XVIII. Clara T., aged 4. This case was the sister of the child whose case I have already commented on, who recovered after suffering from

brain symptoms for three or four weeks. This child was as bad as her brother on admission, groaning and semi-conscious, but unfortunately was four years younger. I gave her a small dose (500,000 bacilli) on the second day after her admission, but within three days the child had died without regaining consciousness. There were no rose spots nor enlargement of the spleen, but as the brother's blood reacted positively to Widal's test I have no doubt that this case was typhoid also.

The next death I have to relate is perhaps of the greatest interest of all, because it illustrates what, in my opinion, the vaccine treatment will do and what it will not.

Case XIX. George E., aged 23 years. On the second day after admission, in view of the severe haemorrhage from which he had already begun to suffer, I gave him only one million typhoid bacilli, i. e. half a dose. The 5 c.c. of diphtheria antitoxin given the day before was to see if horse-serum would check the haemorrhage of typhoid fever. Four days later, when the temperature had reached a lower level, I repeated the dose of one million. The day after this he was clamouring for something to eat, and this hunger, together with the lower
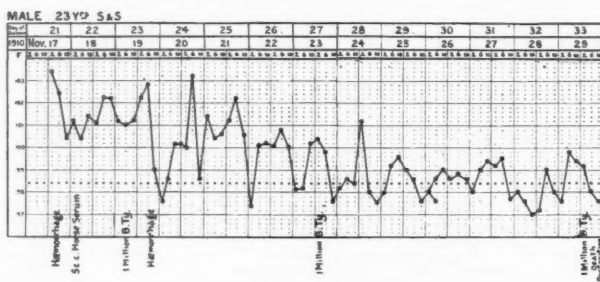

Case XIX.

temperature, continued to the end. On the afternoon of the day of his death his abdomen was slightly distended. He complained of abdominal pains at times and his tongue was coated and dry and he was very anxious to have some tea. I repeated the injection of one million bacilli, and shortly after that—so shortly that it should be in no way connected—he had a violent attack of abdominal pain, and I am now morally certain that the bowel perforated, for he died a few hours later. What I think the vaccine did was to reduce the temperature to a practically normal level. What it failed to do was to bring the ulceration of the bowel to an end or to save him from perforation, and Chantemesse notes particularly that of his deaths perforation is proportionately more frequent than in cases not treated with his serum. The inference I draw from this is that neither serum treatment nor vaccine treatment will save patients from perforation, possibly because an added infection is concerned.

Case XX. Arthur B., aged 33 years. To complete my death roll I relate this case : a man who at first showed no signs of enteric fever, and whose blood failed to give Widal's reaction. After being in hospital seven days there began what we at the time considered the typical rise of temperature of typhoid fever, two days previously some slight headache having been complained of, and on the day previously headache, backache, and scalding micturition. On the sixth day of the raised temperature I injected two million typhoid bacilli, although the patient was suffering at the time from albuminuria and haematuria. Two

days after this he began vomiting, the albuminuria increased, and there was a great deal of blood in the urine; he was suffering considerably from diarrhoea, and four days after the injection there was suppression of urine followed by the man's death. If this was really an attack of typhoid fever—and not of acute nephritis following some other disease, probably influenza—the incubation period was of the shortest.
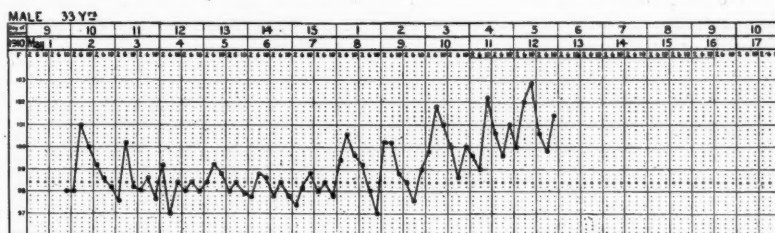
Case XX.

This man's infant son, isolated at the same time as suffering from enteric fever, recovered, but is not included in my typhoid fever cases, as Widal's reaction was negative and there were no rose spots nor enlargement of the spleen.

Case XXI. William A., aged 37 years. I have two more charts which I think deserving of special mention, because they represent my transition between the spacing of doses which I now practise and the spacing with which
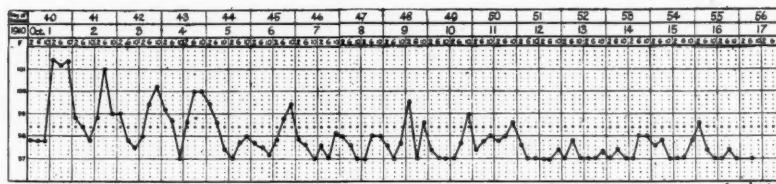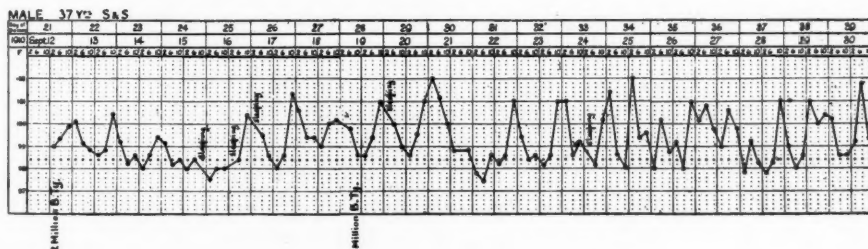
Case XXI.

I started. The first of these cases I re-injected with half the original quantity after seven days, when a rise of temperature suggested that possibly a relapse might be beginning. I did not repeat the injection because the case ran a rather

uneventful course in spite of the failure of the temperature to come down to normal.   There was an improvement on the thirty-fourth day, or six days after the second injection, and that was the point when a third injection should have proved useful.   This case represents   practically   the   first   shortening   of   the interval between injections.

Case XXII.   Thomas W., aged 14 years.   The second case was admitted on the eighth day with a sore over the middle of the sacrum and muttering delirium at night.   He received one million bacilli on admission on the eighth day, and on the twelfth day there was a definite improvement.   A further

Case XXII.

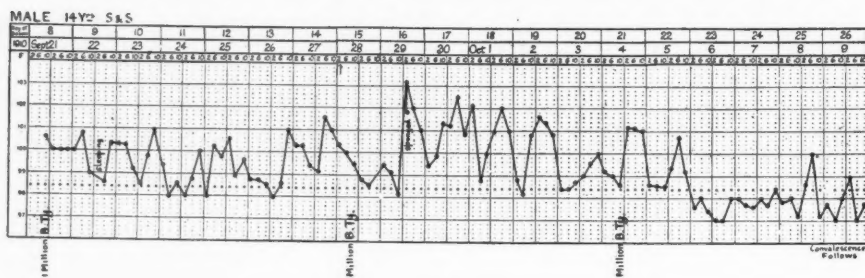injection was given on the fifteenth day, and this seemed to be followed by a negative reaction lasting two or three days, followed by a definite improvement on the twentieth and twenty-first days.   On the latter day he got another million bacilli, and five days later his convalescence had commenced.

These two cases brought me to the conclusion that shorter intervals between the injections were advisable, and that the interval should be about four or five days, with an outside limit of six.   Acting on this principle I find that my more recent cases are doing very well when treated as follows :—If the case appears to be a severe one, and especially if it be of the cerebral type and has muttering delirium, I give half the ordinary initial dose, that is to say, one million bacilli to an adult and proportionately less to children.   If on the other hand the case seems not unduly ill, and especially if it is admitted within the first fourteen days, I give two million bacilli on admission to an adult, and proportionately less to children.

In the less severe cases the initial dose of two millions is the largest which is given throughout the disease, and the second and subsequent injections are of one million bacilli only.   I think one of the cases, where there was a relapse, makes it advisable, even if the temperature has fallen to normal within five days after the first injection, or has assumed a convalescent type, to give at least one re-injection with a view to preventing relapse.   So none of my cases now get less than two injections unless the case is of such a serious nature as to kill them before the fifth day after admission.   Statistically, there has been no improvement of our death-rate.[1]   I should like to point out

[1] 1911, 15 control cases, not injected; 3 deaths—case fatality 20 per cent.   40 cases, vaccine treatment; 5 deaths—case fatality 12·5 per cent.

that of the nine deaths one died before I had sufficient experience with the spacing of doses, one had started with haematuria and nephritis before he got an injection, and also may be reckoned with five others who died within five days of receiving a dose of vaccine. In one of the papers that I have read on the subject, cases dying within a week after admission to the hospital are described as fulminant cases, the inference being that no one can expect to cure such. If I thought myself justified in following this example I should only have two unaccountable deaths—one of whom received vaccine at too long intervals and the other who died from perforation, and my statistics would be nearly as good as I yet hope to see them. I have, however, a very great abhorrence of anything that can be criticized as manipulation of statistics, and apart from statistics I think a great deal can be claimed for the vaccine treatment, seeing that it seems to make average cases mild, severe cases into average cases, and it is only the very worst cases that it does not affect favourably, and to this rule the exceptions are under 2 per cent.

One of the difficulties of the treatment in the cases beneficially affected by vaccine is that the patient begins to be hungry before his tongue justifies any material increase in his diet, and in haemorrhage cases long before the bowel is likely to be strong enough to bear the diet which the patient desires.

Of this I feel sure, that I should now not be justified in withholding the vaccine treatment from any case of typhoid fever I came across, for it is impossible to foretell how severe an individual case is going to be; and even with the severe cases, by administering smaller initial doses of vaccine, there is reasonable prospect of safety, and the patient is none the worse for having received the vaccine.

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APPENDIX.

Here are included cases of typhoid fever injected during 1910, completing the series, with the exception of three cases whose charts have been lost. Of these three one was a moderately severe case and two severe cases. All these cases recovered.

Notes of thirteen mild cases: the first four had proper spacing, the remainder one injection only, in chronological order.
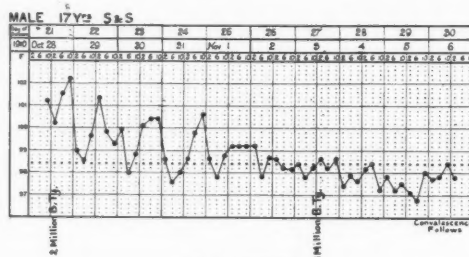
Case XXIII.

Case XXIII. Sidney H., aged 17 years, admitted Oct. 28, 1910. (?) twenty-first day (not well twenty-one days, confined to bed fourteen days). Many rose spots, spleen enlarged. 2 *million B. typh.*

Nov. 3: apparently convalescent. 1 *million B. typh.*
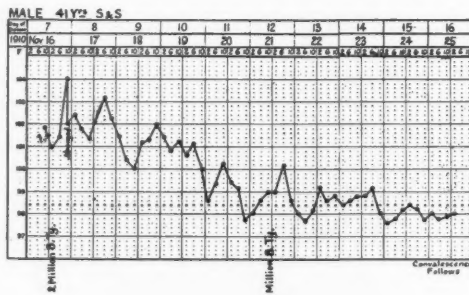
Case XXIV.

Case XXIV. Joseph L., aged 41 years. Nov. 16, 1910: admitted sixth day of disease ; rose spots and enlarged spleen. 2 *million B. typh.*

Nov. 19: enteric fever smell.

Nov. 21: seems much better. 1 *million B. typh.*

Case XXV. Hiram B., aged 19 years, admitted Nov. 26, 1910, the fourteenth day of disease; typical rose spots and enlarged spleen. *2 million B. typh.*

Nov. 27: some abdominal pain.

Nov. 29 to December 6: diarrhoea.

Dec. 1: 1 *million B. typh.*

Dec. 9: noted convalescent for first time, although temperature continued as on Dec. 4 and 5.
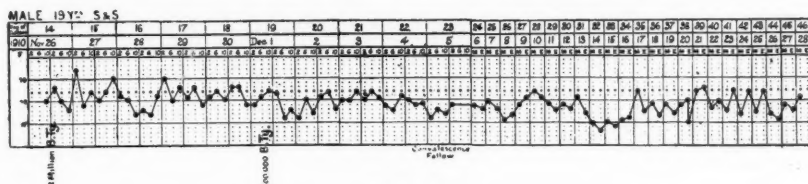
Case XXV.
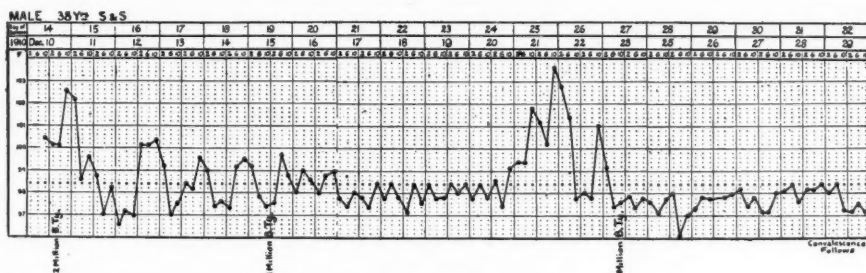
Case XXVI.
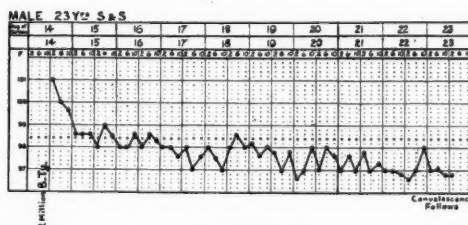
Case XXVII.

Case XXVI. William Henry K., aged 38 years, admitted Dec. 10, 1910, the fourteenth day; rose spots and enlarged spleen. *2 million B. typh.*

Dec. 15: 1 *million B. typh.*

Dec. 21: rise of temperature appeared to be caused by ingestion of boiled bread and milk, which always caused him nausea when in health.

Dec. 23: 'to make sure'. 1 *million B. typh.*

Jan. 2, 1911: 'convalescent.'

Case XXVII. John Henry C., aged 23 years, admitted May 14, 1910, the fourteenth day of disease; *2 million B. typh.* injected.

May 15: typical rose spots, enlarged spleen.

June 4: convalescent.

Case XXVIII.   Arthur S., aged 9 years, admitted April 1, 1910, fifteenth day of disease.

  April 3 : 1 *million B. typh.* injected.
  April 8 : convalescence began.
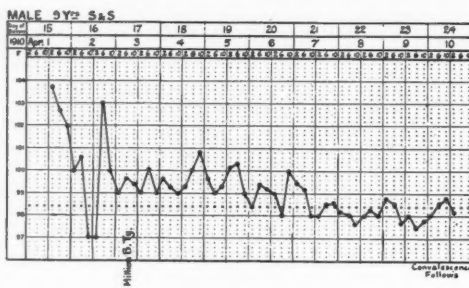
Case XXVIII.
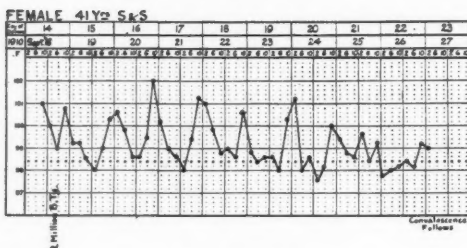
Case XXIX.
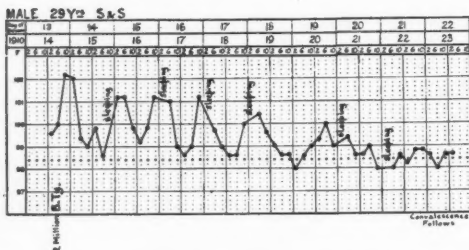
Case XXX.

Case XXIX.   Clara O., aged 41 years, admitted Sept. 18, 1910, the fourteenth day ; typical rose spots, enlargement of spleen.   2 *million B. typh.*

  Sept. 20 : feels better.
  Sept. 24 : convalescence begins.

Case XXX.   William James W., aged 29 years, admitted Sept. 14, 1910, the thirteenth day; typical rose spots; enlargement of spleen; pain in head and back.   2 *million B. typh.*

  Sept. 17 : no pain.
  Sept. 23 : parotitis left side, which recurred on October 8 ; no rise of temperature caused thereby.

Case XXXI.   James O., aged 43 years, admitted Sept. 18, 1910, the fifth day ; 2 *million B. typh.*, because son has undoubted typhoid.

    Sept. 19 : spleen enlarged.

    Sept. 25 : blood from right ear ; Widal negative.

    Sept. 28 : smells of enteric.

    Oct. 3 : blood from left ear ; Widal positive.
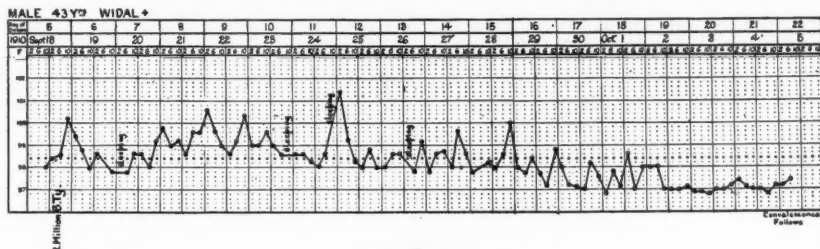
Case XXXI.
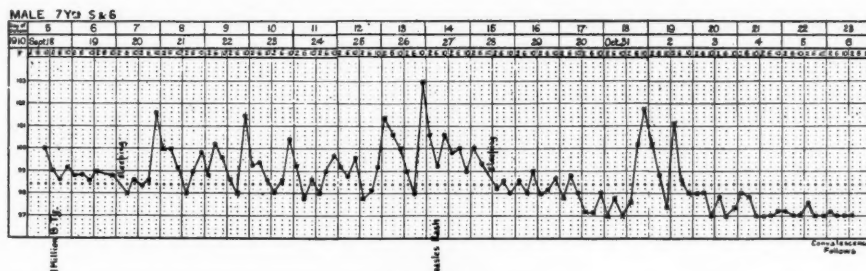
Case XXXII.
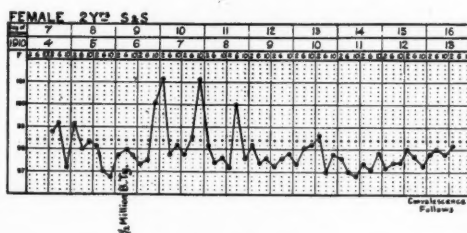
Case XXXIII.

Case XXXII.   John O., aged 7 years, admitted on Sept. 18, 1910, the fifth day ; 1 *million B. typh.* the only injection.

    Sept. 23 : tenth day, Widal reaction negative.

    Sept. 25 : typical rose spots and enlarged spleen.

    Sept. 27 : morbilliform rash, certainly not measles ; rash very irritable ; faded two days later.

Case XXXIII.   Doris H., aged 2 years, admitted Nov. 4, 1910, the seventh day of disease.

    Nov. 6 : typical rose spots seen. $\frac{1}{2}$ *million B. typh.*

    Nov. 7 : typical rose spots seen ; spleen just palpable.

Case XXXIV. John Henry C., aged 18 years, admitted Nov. 5, 1910, the fifth day of disease, because brother, whose chart had been lost, was moderately severe and typical case of typhoid. *2 million B. typh.*

Nov. 6 and 7 : typical rose spots and enlargement of spleen.
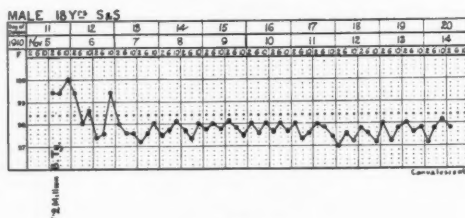
Case XXXIV.
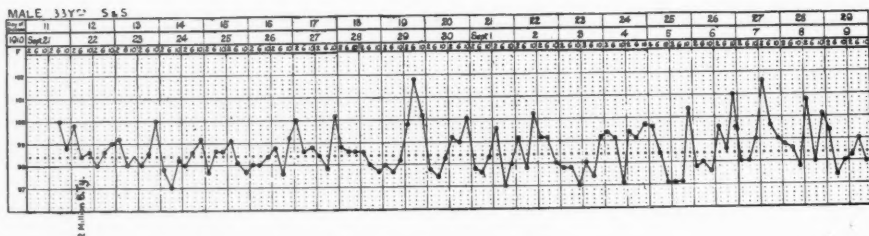
Case XXXV.

Case XXXV. Thomas William M., aged 33 years, Sept. 22, 1910, twelfth day of disease ; typical rose spots, enlargement of spleen. *2 million B. typh.*

Sept. 27 : 1 million more B. typh. should have been injected at this point. Had bread-crumb in mutton broth Sept. 26 and diet was gradually increased till on Oct. 8 he had fish and on Oct. 14 boiled mutton. On Oct. 21 the diet was reduced to milk and soda-water only till Oct. 24, when 'feeding' was again resumed.

*12 medium cases with notes ; first two cases proper spacing, remainder in chronological order.*

Case XXXVI. Joseph A., aged 49 years, admitted Nov. 15, 1910, the fourteenth day of disease ; rose spots and enlarged spleen. *2 million B. typh.*

Nov. 17 : slight phlebitis of right femoral vein.

Nov. 19 : pain in calf of right leg, which is soft and only slightly swollen.

Nov. 20 : 1 *million B. typh.*

Nov. 21 : very hungry ; swelling on inner side of right thigh.

Nov. 26 : abscess opened inner side of right thigh.

Dec. 11: leg very painful; extension of abscess cavity downwards and backwards.

Dec. 12: counter-opening made.

Dec. 16: oedema of right foot; incision into tender and boggy spot on outer side of right calf muscles.

Dec. 18: abscess deep to the calf muscles opened through incision of Dec. 16.

Dec. 19: free discharge from abscess. Convalescence follows.

Dec. 10–18: intermittent fever caused by retained pus. No further injection given after Nov. 20 as the subsequent symptoms were due to the phlebitis, &c., and not to enteric.
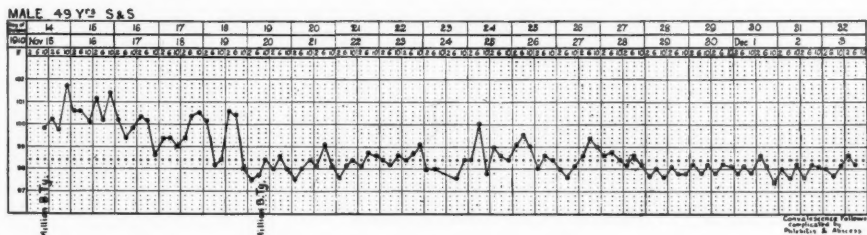
Case XXXVI.
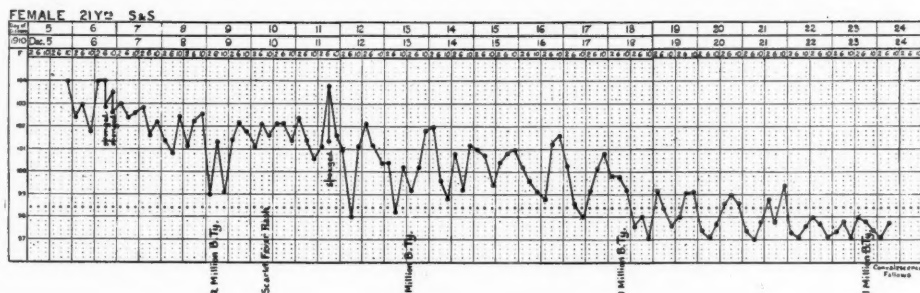
Case XXXVII.

Case XXXVII. Nurse S., aged 21 years, warded Dec. 5, 1910, with temperature of 104°, on the fifth day of disease.

Dec. 8: typical rose spots and spleen.

Dec. 9: erythematous rash chest and neck. *2 million B. typh.*

Dec. 10: rash undoubted scarlet fever.

Dec. 13: 1 *million B. typh.*

Dec. 18: 1 *million B. typh.*

Dec. 19: rapidly improving.

Dec. 23: to avoid relapse; last injection of 1 *million B. typh.* Convalescence followed.

Case XXXVIII. Jessie H., aged 6 years. Cross infection; started with enteric fever thirty-eighth day of scarlet fever; rose spots and enlarged spleen. Injected with ½ *million B. typh.* twenty-fourth day of enteric fever (Jan. 17). Four days later a little aching pain at site of injection, but convalescence beginning.
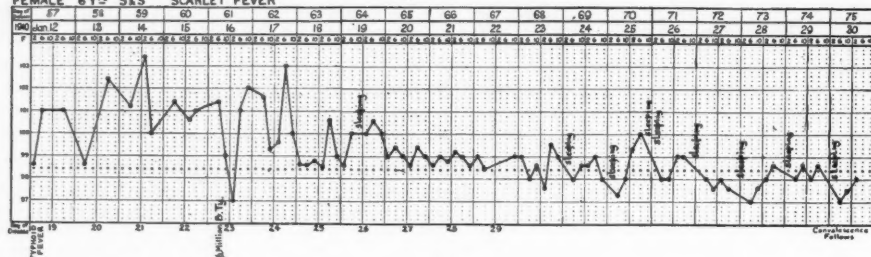
Case XXXVIII.
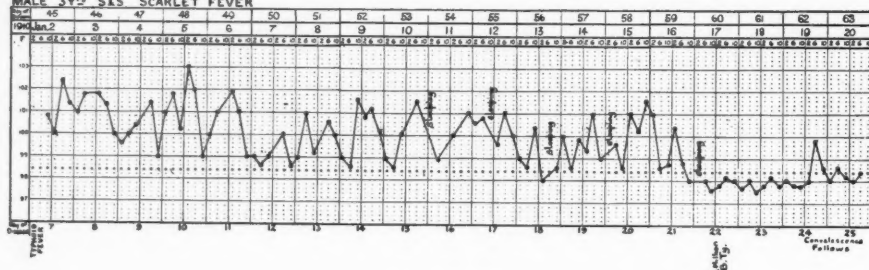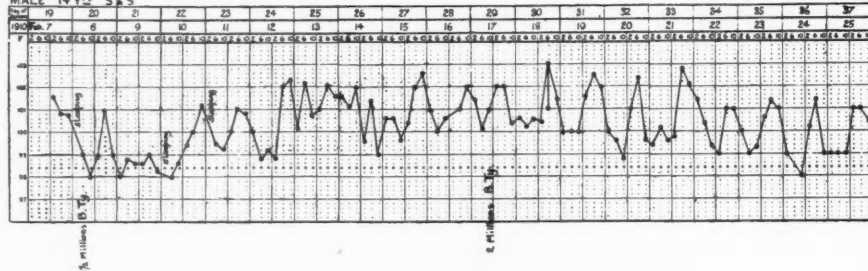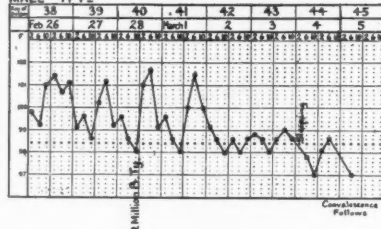
Case XXXIX.

Case XL.

Case XXXIX. William W., aged 3 years. Cross infection; enteric fever started on thirty-ninth day of scarlet fever; typical rose spots and enlargement of spleen on sixteenth day of enteric fever.

½ *million B. typh.* injected on the twenty-second day of enteric fever (Jan. 17); convalescence started three days later.

Case XL. Henry B., aged 14 years, admitted Feb. 7, 1910, the nineteenth day of disease; spleen enlarged, no rose spots.

Feb. 8: specimen of blood from ear, Widal's reaction negative. 1½ *million B. typh.*

Feb. 9 and 10: typical rose spots appeared.

Feb. 14: pain in arms and legs (? rheumatic; relieved by salicin).

Feb. 17: hungry; no pain. 2 *million B. typh.*

Feb. 24: tongue clean.

Feb. 28: 2 *million B. typh.*

Mar. 3: convalescence begins.

(N.B.—Intervals too long; second and third doses too large.)
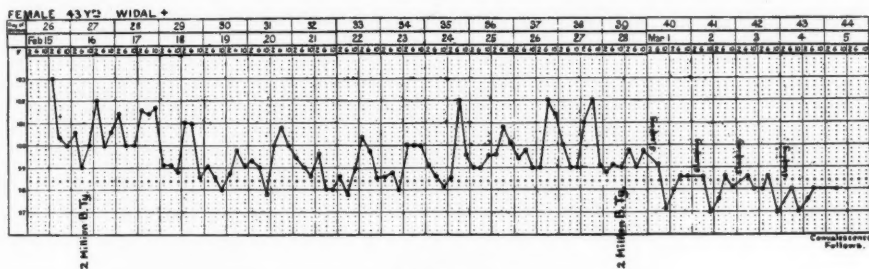
Case XLI.
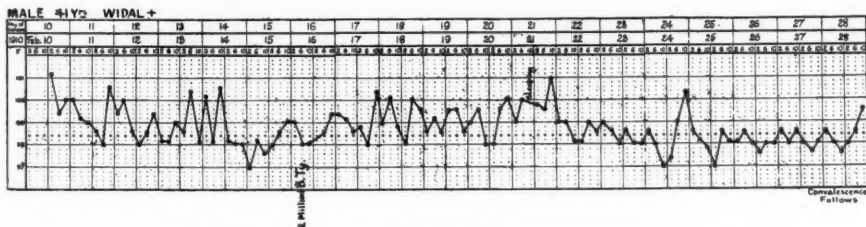
Case XLII.

Case XLI. Mary B., aged 43 years, admitted Feb. 15, 1910, the twenty-sixth day of disease; peasoup stools, enlarged spleen.

Feb. 16: 2 *million B. typh.*

Feb. 19: improvement in temperature.

Feb. 26: severe abdominal pain.

Feb. 28: 2 *million B. typh.*

Mar. 4: beginning of convalescence.

Case XLII. Albert M., aged 41 years, admitted Feb. 11, 1910, on tenth day; no rose spots, spleen not felt, pneumonia at left base.

Feb. 13: Widal negative.

Feb. 15: Widal positive.

Feb. 16 : 2 *million B. typh.* injected.

Feb. 20 : felt better.

Feb. 25 : so improved that no further injection given.

Mar. 1 : convalescence began.

Case XLIII.   Annie Elizabeth S., aged 5 years, admitted Mar. 16, 1910, eleventh day of disease ; typical rose spots, spleen enlarged, bronchitic râles both lungs.   ½ *million B. typh.* injected.

Mar. 25 : very fretful and still ill, though temperature normal or below.

Apr. 3 : really better; appetite returned.
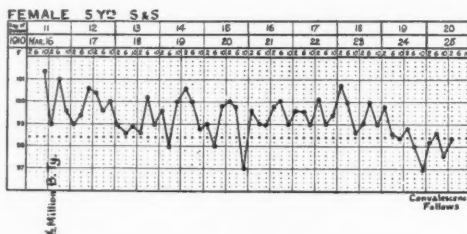
Case XLIII.
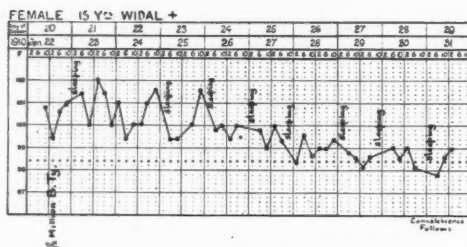
Case XLIV.

Case XLIV.   Mary A., aged 15 years, admitted Jan. 22, 1910, twentieth day of disease ; no rose spots, spleen not felt; Widal's reaction positive ; abdomen distended.   1½ *million B. typh.* injected.

Jan. 21 : heart galloping.

Jan. 22 and 23 : abdominal pain.

Jan. 25 : improving.

Feb. 1 : convalescence began.

Case XLV.   James O., aged 13 years, admitted Sept. 12, 1910, on twelfth day of disease ; typical rose spots, enlargement of spleen, depressed and thinks he is going to die because twin sisters died at home of typhoid on Sept. 10, 1910. 2 *million B. typh.*

Sept. 15 : feeling well.

Sept. 17 : complains that he ' does not feel poorly and *is* hungry '.

(Here a further injection of 1 million B. typh. should have been given.)

Sept. 25 : Widal positive.

Oct. 5 : convalescence begins.

Case XLVI.   Fred G., aged 5 years.   Diphtheria cross-infected with typhoid.
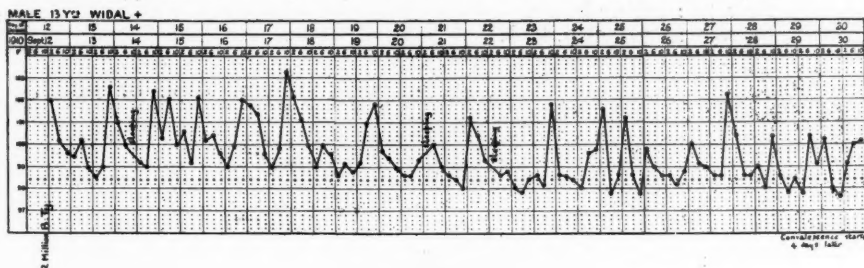
Case XLV.
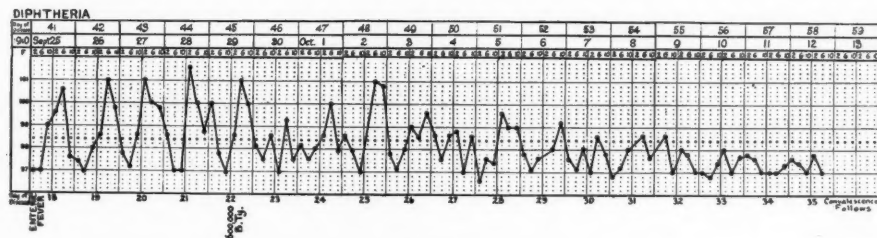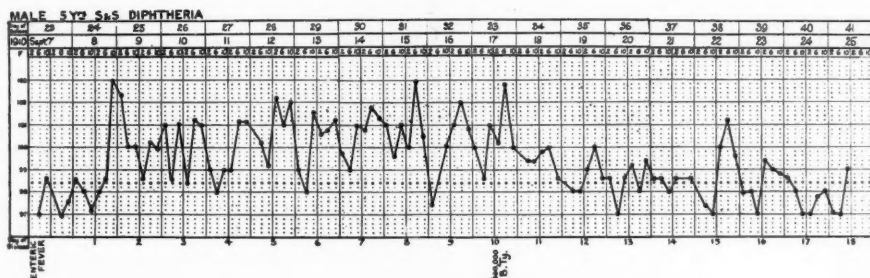
Case XLVI.
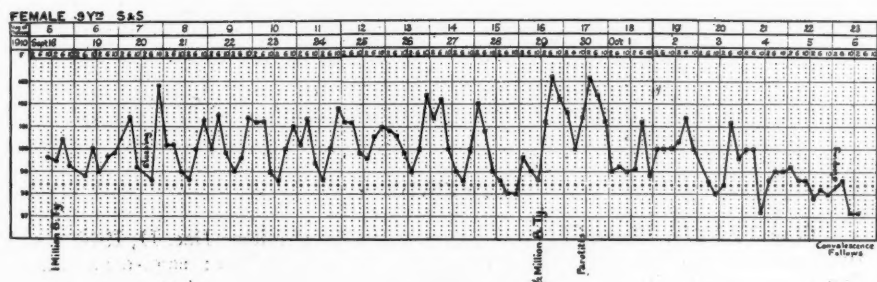
Case XLVII.

Sept. 17, 1910 : rose spots and enlarged spleen.   600,000 *B. typh.*

Sept. 20 : taking better.

Sept. 29 : 600,000 *B. typh.*

Sept. 30 : distinct improvement.

    Case XLVII.   Elizabeth O., aged 9 years, admitted Sept. 18, 1910, on fifth day of disease. 1 *million B. typh.*

Sept. 22 : very hungry ; moist tongue slightly coated.

Sept. 23 : spleen enlarged ; Widal's reaction negative.

Sept. 26 : three or four typical rose spots.

Sept. 29 : ½ *million B. typh.*

Sept. 30 : parotitis right side.

Oct. 6 : convalescence begins.

                          (Interval too long.)

6 severe cases with notes ; first case properly spaced, other cases in chronological order.

Case XLVIII.

    Case XLVIII.   Laomi J. (male), aged 22 years, admitted Dec. 11, 1910, the twenty-first day of disease. Rose spots and enlarged spleen ; semi-conscious, lips poor colour. *Lungs,* a few râles at right apex. *Heart,* first sound at base very fair ; no murmur. Retention of urine. 1 *million B. typh.*
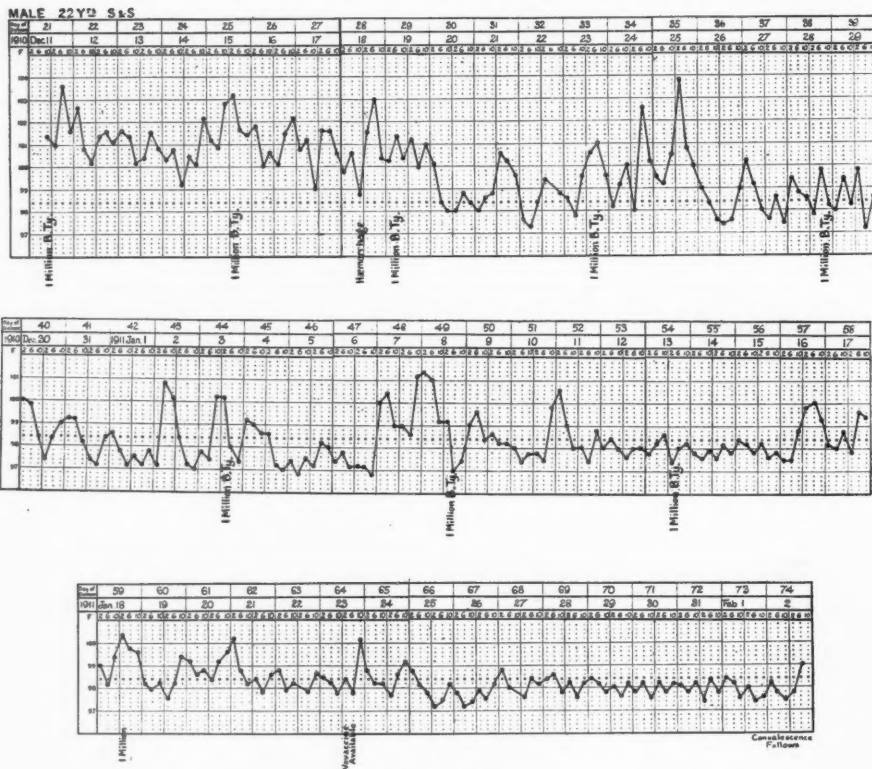
Dec. 15 : much more sensible.   1 *million B. typh.*

Dec. 18 : haemorrhage from bowel, approximately a pint.

Dec. 19 : 1 *million B. typh.*

Dec. 21 : very restless, looks very ill, no pain ; lies on side.

Dec. 23 : 1 *million B. typh.*

Dec. 25 : temp. 103° at 2 p.m. ; reported to be brighter.

Dec. 28 : hungry.   1 *million B. typh.*

Dec. 31 : tongue thickly-coated still ; constipated.

Jan. 3, 1911 : abdominal pain over pubic region ; constipated ; abdomen soft.   1 *million B. typh.*

Jan. 6 : very hungry ; tongue almost clean.

Jan. 8, 13, and 18 : 1 *million B. typh.* on each date, with steady improvement.

(Inoculation on Dec. 19 not followed by return of haemorrhage.)
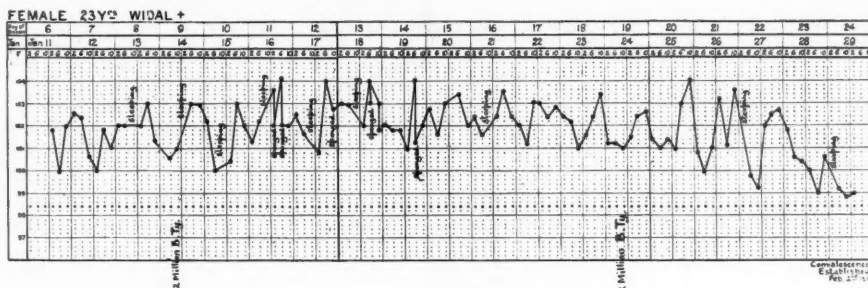
Case XLIX.

Case XLIX.   Margaret Ellen J., aged 23 years, admitted Jan. 11, 1911, the sixth day of disease.

Jan. 13 : Widal's reaction reported positive ; rose spots and enlarged spleen.

Jan. 14 : 2 *million B. typh. injected.*

Jan. 24 : 2 *million B. typh. injected.*

Jan. 29 : temperature improving.

Feb. 2 : convalescence began.

Case L.   Fred P., aged 5 years, admitted Feb. 19, 1911.   Rose spots and enlarged spleen.   *Heart* dilated and galloping.   *Lungs*, dullness and tubular breathing left base, coarse râles left axilla.   ½ *million B. typh.*

Feb. 20 : screaming all previous night ; drowsy.   *Heart* slightly improving.

Feb. 22 : head tends to be retracted ; appearance suggests meningitis. *Heart* less dilated ; swallows badly ; cries out in sleep.

Feb. 23 : head retracted ; pupils dilated.

Feb. 26 : twitching at times ; swallows better.   *Heart* improving.

Feb. 28 : 1 *million B. typh.*

(¼ million B. typh. on 23rd would have been more satisfactory.)

Mar. 1 : some nystagmus.

Mar. 3 : still nystagmus ; seems more sensitive to pain.

Mar. 6 : more conscious ; sleeping better, less pain ; takes better.

Mar. 9 : beginning of convalescence.

R 2

Case LI. Tom L., aged 45 years, admitted Aug. 11, 1910, twenty-first day of disease.

History of previous attack of enteric fever in 1887 at Gibraltar.

Delirious at nights; very numerous rose spots. 1 *million B. typh.* on admission.

Very deaf three weeks; haemorrhage from bowel before admission.
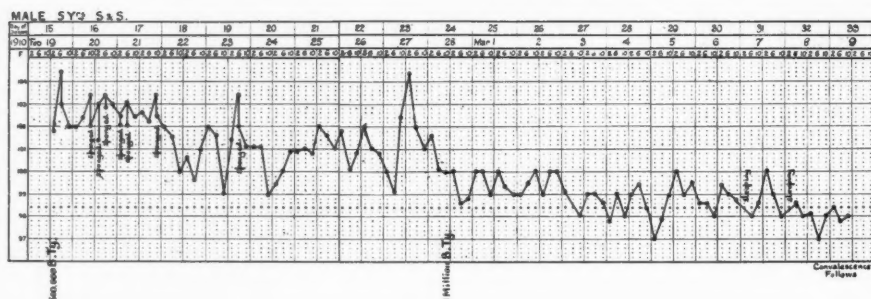
Case L.
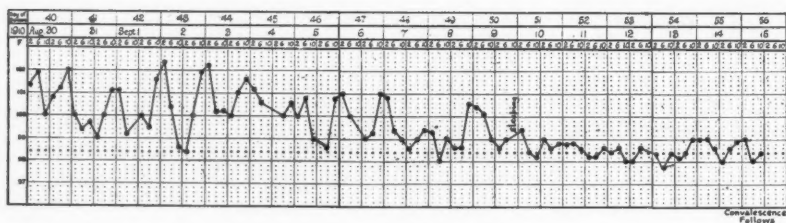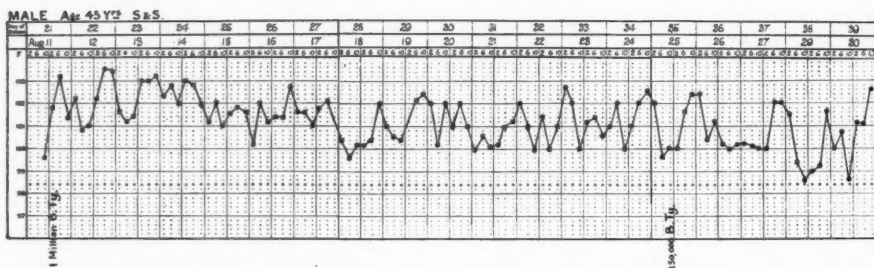
Case LI.

Aug. 23 : still rambling at times ; deafness and strength of heart improving.

Aug. 25 : ¼ *million B. typh.* injected.

Aug. 31 : temperature lower level ; pulse improving ; tongue dry and furred.

Sept. 10 : tongue moister, beginning to clear ; hungry.

Sept. 11 : beginning of convalescence.

(N.B.—Five days after second injection real improvement started.)
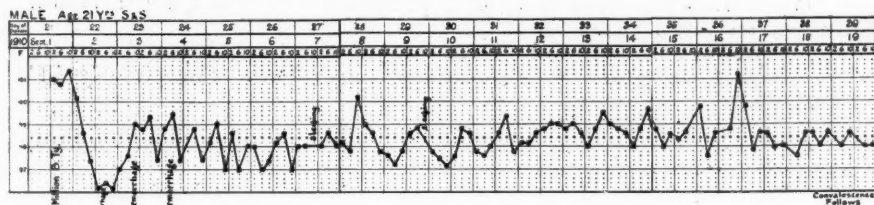
Case LII.
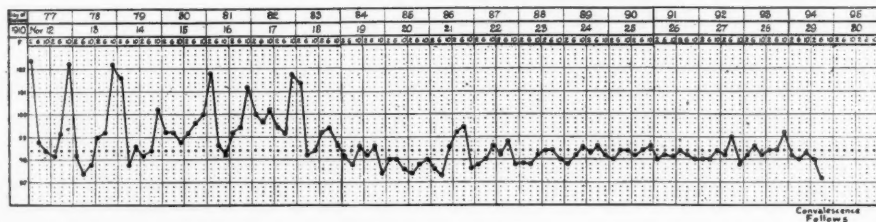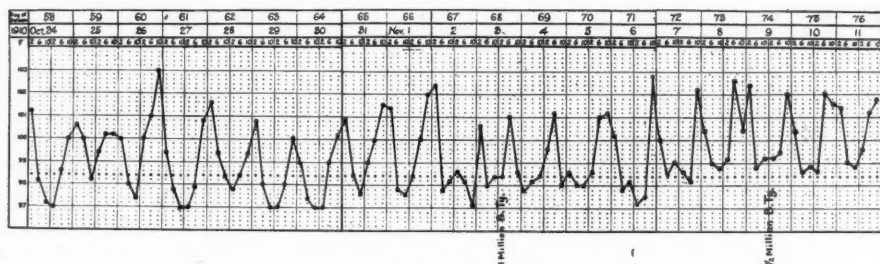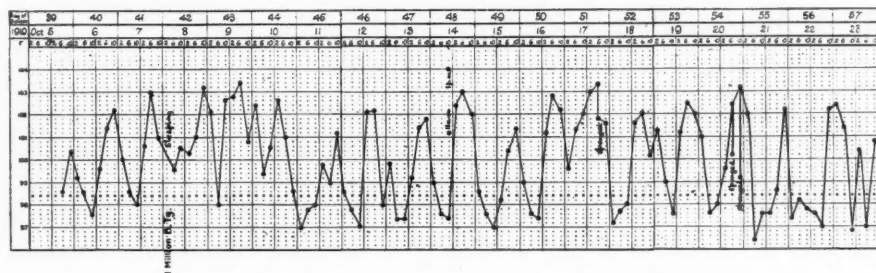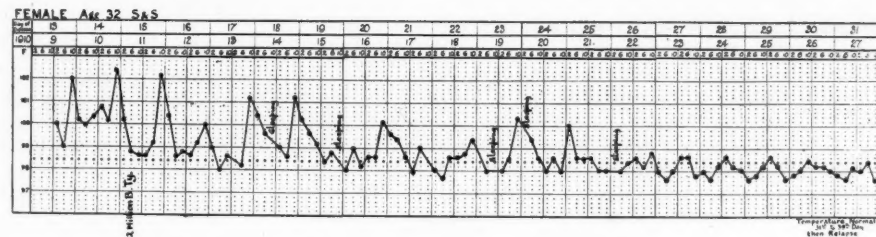
Case LIII.

Case LII. John James D., aged 21 years, admitted Sept. 1, 1910 : typical rose spots ; ? spleen. 2 *million B. typh.*

Sept. 11 : spleen enlarged ; very hungry, but looks weak and ill.

Sept. 2, 3, 6, and 8 : haemorrhage from bowel. 'Dangerously ill' Sept. 2–11.

Case LIII. Georgiana W., aged 32 years, admitted Sept. 9, 1910, thirteenth day of disease ; peasoup stools.

Sept. 11 : spleen enlarged ; rose spots. 2 *million B. typh.* injected.

Sept. 13 : feels better.

Sept. 15 : improving (here the injection of 1 million more B. typh. would possibly have saved the subsequent relapse).

Sept. 26 : convalescence seems to begin. The temperature remained normal until Oct. 5, thirty-ninth day.

(The normal temperature from thirty-second to thirty-ninth day is omitted from the reproduced charts.)

Oct. 5 : relapse begins.

Oct. 8 : fourth day of relapse. 1 *million B. typh.* injected.

Oct. 21 : onwards, except for temperature and gradually failing strength, the patient did not seem very ill.

Nov. 2 : pain over caecum.

Nov. 3 : 1 *million B. typh.* injected.

Nov. 9 : no pain. $\frac{1}{2}$ *million B. typh.* injected.

Nov. 14 : improving.

Nov. 19 : convalescence begins.

ON MYOTONIA

By T. WARDROP GRIFFITH

With Plates 9–13

THE affection known as Thomsen's disease is of such rarity that it is desirable that all cases which come under the notice of members of our profession should be put on record, even when the symptoms conform in all respects to those of the classical example described by Thomsen as occurring in himself, or to those of the cases which have been put on record in this country by Buzzard (4), Hale White (16), and others. So far as I have been able to ascertain, the only cases which have been recorded in this country since the year 1890 are the four occurring in members of the same family, which were shown by Dreschfeld (5) at the Manchester Medical Society and briefly noted in the *Lancet* in 1905, and the two shown by Risien Russell (13) at a meeting of the Neurological Society in March, 1900.

The three cases which form the earlier part of this communication occurred in members of the same family, and the symptoms of the affection in the case of two of them, transient as they were in one, and greatly diminishing in severity and ultimately disappearing in the other, merit special attention.

In most of the cases on record it has been specifically mentioned that the muscular development of the patient was good, and in some cases very pronounced. In Strümpell's case (9) there is said to have been a true muscular hypertrophy, the strength of the patient being in proportion to the muscular development. That those the subject of the affection were able to perform hard work and take prolonged exercise without fatigue, after the initial stiffness of the muscles had passed off under the influence of movement, may be regarded as evidence that the enlargement of the muscles in those particular instances was not of the nature of a pseudo-hypertrophic change, for that is associated with weakness.

Vigoroux (15) describes a case of Thomsen's disease which also presented the signs of pseudo-hypertrophic muscular palsy. The enlarged muscles were weak, and the writer regards the case as an example of two separate diseases attacking the same patient. One misses, however, any mention of that wasting of certain groups of muscles, such as those of the anterior and posterior axillary folds, which occurs almost invariably in pseudo-hypertrophic palsy, nor was any microscopical examination made of the muscles. The knee-jerks were increased, and this he associates with the myotonia, though he says the symptom

' n'a pas été signalé dans cette affection '.   In commenting on the case, Vigoroux
mentions that enlargement of the muscles had been noted by others, and refers to
the paper of Ballet and Marie (1).   These writers in 1883 discussed the various
cases of Thomsen's disease on record at that time.   In the case they themselves
describe, though they comment on the good muscular development of the patient,
they refuse to employ the term 'hypertrophy' in view of the fact that the man
was of considerable stature and of strong build.   They quote three cases of
Seeligmüller's in which the muscles are described as being respectively ' athletic
and hard as wood even when at rest ', ' très développés, durs, présentant comme
des échelons à la palpation,' and in the third case ' voluminous and hard as
stone '.   Though there is no mention of muscular weakness in these cases the
description of the muscles recalls the condition found in pseudo-hypertrophic
palsy.   The writers also mention a case of Bernhardt's in which, though the
consistency of the muscles was not increased, there was extraordinary develop-
ment of the muscles of the lower extremity ; here also we are reminded of the
condition found in pseudo-hypertrophic palsy, for it is said that the muscular
force did not correspond with the athletic appearance of the man, though it was
fairly good.   Especially noteworthy is the observation of Petrone, also mentioned
by these writers, that in a lad of fifteen with well-marked myotonia, whose calves
measured 31 cm., a portion of the biceps flexor cruris was found on examina-
tion to be normal, though the observation would have been a more valuable one
had the portion of muscle examined been taken from the gastrocnemius, for there
is no mention of the size of the thigh.

In the article on the myopathies in *Allbutt and Rolleston's System*, Batten (2)
describes under the name of myotonia atrophica, a term suggested by Rosso-
limo (12), a condition ' characterized by the rare association of muscular atrophy
with a slow relaxation of muscles after voluntary contraction '.   He mentions
that Noguès and Sirol (10), as well as Hoffmann (8), had previously described
the same combination of symptoms under the title of Thomsen's disease with
muscular atrophy.   Rossolimo credits Schönborn with having been the first to
point out the association of muscular atrophy with myotonia.   Neither in the
paper of Rossolimo nor in that of Noguès and Sirol is there mention of any of
the muscles being enlarged.

The second part of my paper deals with a case which may prove of interest
in connexion with these observations, presenting as it does the symptoms of
myotonia in a pronounced form, along with marked atrophy of some groups
of muscles and an enlargement of those of the calves.   In this case there was
much from the clinical side to make one suspect that the symptoms of myotonia
were associated with those of pseudo-hypertrophic palsy ; but the increase in the
knee-jerks, the age of onset, the distribution of the atrophy, and especially the
absence of wasting of the lower part of the pectoralis major made one hesitate
to conclude that this was the case.   The histological examination appears
definitely to exclude this affection and to show that there was a real enlarge-
ment of the muscular fibres, and that any increase in the general mass of the

muscle was not due to a fatty or fibrous infiltration. Following Rossolimo and modifying his title to the special conditions met with in my patient, I venture to call the case one of myotonia atrophica et hypertrophica.

I. Cases of Thomsen's Disease.

S. C., a young man of thirty-four, came to my out-patient department in 1901 complaining of a peculiar stiffness of his muscles, which led to an immediate and very easy diagnosis of myotonia congenita. In investigating his symptoms I was careful to avoid putting leading questions, at least in the first instance, but the clear way in which he explained his disabilities and illustrated his difficulties led me to suspect that he had been trained in their appreciation by having been the subject of a clinical demonstration. This, however, was not the case; on the contrary, he had never consulted any one about the affection, nor had the other two members of his family who were affected done so.

On leaving school he was employed in a hatter's shop and acted as salesman till he was 22 years of age. He was then employed in a public-house for some twelve years. Having saved a little money he started business on his own account, but in a short time he failed and found himself so handicapped in making a living that he came to the General Infirmary at Leeds to see if anything could be done to improve the condition.

He stated that the symptoms had been present as long as he could recollect, and that, though he never was free from them, they varied considerably in severity. He remembered that when playing with his fellows at school, he had furtively to exercise his legs before attempting to run, and that he was at a disadvantage in any game which called for alertness in movement. The symptoms were usually worse in cold weather and if from any cause he had abstained from taking food longer than usual. His general health was good in every way.

As already mentioned, he described the condition with very little prompting. Thus he said that when at rest for any length of time and called upon for any sudden movement he could not carry it out at once; that the muscles felt stiff for a time, but that soon he was able to use them perfectly well. Spontaneously he gave examples: in getting on to a tramcar in motion, which he attempted to do only when it was moving slowly, he was in the habit of working his legs about in anticipation of its reaching the spot where he was standing, while he never ventured to get off a moving car because 'the leg on which he did not alight would not come forward' and he would fall. Here I may say I suspected he had been studying the *Guy's Hospital Reports* for 1889 (16), but in this I did him an injustice, and after all, the inability to get off a tram in motion must, to a young man, be a symptom worthy of note. He also mentioned that he played the violin a little but always experienced some difficulty in starting. He could ride a bicycle or tricycle, though he had some difficulty in mounting, but usually ended his career on the former by falling off.

He believed that all his muscles, by which of course he would only include the voluntary muscles, were affected. Sometimes the muscles of the jaws were stiff, he said, and occasionally in beginning to speak his tongue would be difficult to move. On the other hand, he never had had any difficulty in swallowing or in breathing; the sphincters were normal and there had been no difficulty in the act of coitus.

I asked him suddenly to get up and walk to the door. On the first effort his feet seemed glued to the floor, then with laboured effort he dragged them forward alternately, the movement becoming easier and easier until in about half to three-quarters of a minute the gait was quite natural and easy, and remained so as long as he kept going, while the same phenomena were elicited by repeating

the experiment after a short period of rest. When the muscles involved in ordinary walking had been rendered capable of normal and prompt relaxation, I got him to attempt suddenly to change his walk into a run, when at once the new muscles employed, and doubtless also the increased action, or it might be the altered combination of the muscles employed, caused him to stumble and incontinently to shoot forward, so that had I not anticipated this and been ready he would have fallen. Repeating this experiment, it was very striking to see the initial difficulty in walking and then the few spasmodic-like jerks when he now with greater care converted his quick walk into a run, which did not become quite natural until he had gone some ten to fifteen yards.

He undressed himself for further examination with apparent ease. I did not notice any impaired action of his fingers when he was unbuttoning his garments, and when I remarked on this he said that occasionally they did stick, and illustrated the usual attitude in which this happened by putting his fingers and thumb in the position required to pick up a pin.

When stripped he appeared to be a man of an unusually muscular build even when his muscles were quite relaxed, which they became when he had been lying at rest for some time. This was the more striking as he had never done any work involving muscular exertion in his life, and the nature of his affection had rendered athletics out of the question.

The girth of his right forearm was $10\frac{6}{8}$ in., that of the left $10\frac{7}{8}$ in.; the girth of the right arm was $11\frac{1}{8}$ in., that of the left $11\frac{3}{8}$ in. He stated that he was a left-handed man for many actions, as for example in throwing a stone, and in regard to this action he said he always had to throw several stones before getting to what he regarded as his normal range, and not infrequently his second attempt would be worse than his first.

A good many experiments were then tried, of which I may mention the results of the following, not necessarily in the order in which they were elicited :—

When his muscles were in a state of very complete relaxation, secured by lengthened repose, passive movements of the limbs carried out with great gentleness did not result in the muscles becoming rigid. On my first trying this experiment I seemed to be led to a different conclusion, but this I found was due to the patient instinctively resisting the passive movements by the action of opposing groups of muscles, which became rigid in the same way as they did after direct voluntary contraction. It is indeed a very difficult thing for any one to let his limbs lie passive in the hands of an examiner, and familiar examples of this will occur to all in the difficulty some patients have in relaxing their quadriceps sufficiently to enable the knee-jerk to be elicited, and in the rigidity of the abdominal muscles when even gentle palpation is tried, a condition which persists in some cases, it may be until long after the patient has apparently given the examiner his complete confidence, and which is quite beyond his control.

When he closed his hand firmly, no matter how short that voluntary effort might be, he had considerable difficulty in opening it; the effort was apparently tremendous and the extension unwilling and slow. All the muscles of the forearm, which, though well developed, were not unduly hard before the voluntary grip, now stood out with extraordinary distinctness and felt very hard to the touch. As a rule it required 15 seconds for extension of the fingers and hands to be completely effected after the first closure of the hand, but succeeding closures were followed by more and more rapidly carried out acts of extension until the movements became normal in every respect and the muscles seemed to regain their normal feeling to the touch. It is mentioned and emphasized in some of the cases recorded, that the extension has been effected first in the metacarpophalangeal, then in the proximal, and last in the distal interphalangeal articulations, but I cannot say that I was impressed by this or that it was in any way

more marked than under physiological conditions, for I think most of us will find that on slowly opening the closed hand the extension of the different joints follows the above-noted sequence. Returning to the point of time when the act of extension was complete after the first closure of the hand, I noted that the following act of closing the hand was carried out quite sharply, and was apparently unrestrained by the rigid condition of the muscles on the back of the forearm, for it must be noted that these muscles as well as those on the front of the forearm contract in the simple act of clenching the hand.

It was very interesting to note the result of a prolonged as contrasted with a momentary voluntary contraction or with one of brief duration. Thus when the patient was directed to grasp his hand firmly and keep it tightly closed for some time it was found that extension could then be effected as rapidly as in a normal individual, and as the result of many observations I found that if the firm contraction were kept up for fifteen seconds the act of extension could be carried out normally.

Experiments on the same lines were carried out in the case of most of the muscles and movements of the body, and generally speaking with similar results. In all cases short and vigorous voluntary contraction was followed by rigidity, which passed off with the simple lapse of time, or on the same contraction being repeated several times. Thus when, lying on his back, he raised himself to the sitting posture by the action of his abdominal muscles and at once lay down again, the musculature of the abdominal wall became extremely obvious, every division of the rectus standing out with the utmost distinctness, and this condition remained for some little time and passed off gradually. On the other hand, when he similarly raised himself about half-way to the sitting posture and kept himself in that attitude, which of course he did by the sustained action of the abdominal muscles, until he felt the strain becoming almost too great to maintain, and then lay down, it was found that the abdominal wall did not present any undue prominence of the muscles, but was soft and natural. Similarly, experiments with flexion and extension of the neck, with rotatory movements of the head and with calisthenic movements of the limbs, all demonstrated the same stiffness of the muscles after brief voluntary contraction.

This contrast in the effects of a prolonged and a brief voluntary effort has not, so far as I have been able to ascertain, attracted the attention of other observers, and it appears to me to be a matter of some importance.

It is stated that the finer movements of the hands and fingers are not affected and that the interossei muscles often escape. It was not so in my patient, though a superficial examination might lead one to think the contrary, especially as he could write a fairly good hand. The following experiment demonstrated that the interossei were affected in the same way as the other muscles of the body and limbs, and provided at the same time an interesting illustration of one of the actions of these muscles. With the fingers extended he was directed to abduct and adduct the fingers alternately; this at first he could only do slowly, but after a few acts of abduction and adduction the movements became rapid and normal in harmony with the foregoing observations. Now it may be observed in going through these movements oneself that the middle finger hardly moves at all, for, as is well known, the interossei act to and from the middle line of this finger. In our patient, therefore, the second and third dorsal interossei, which move the middle finger respectively towards the index and towards the ring finger, were not employed, or if so, only to a very slight extent, in the movements of abduction and adduction which he was directed to perform, with the result that, even when these movements became quite normal and free, movement of the middle finger from side to side had to be slowly and laboriously carried out several times before it could be effected at all quickly.

I desire to emphasize this affection of the interossei because Hale White (16)

says (d), 'the interossei often escape; my patient can write very well'; and again (a), 'the action of the interossei is healthy, so that the patient has no difficulty in writing.' This would seem to imply that ability to write well acquits these muscles of participation in the affection. In some people, however, the interossei are employed only to hold the pen, the movements of which are carried out from the shoulder and elbow, and in many the interossei, though used to assist in the movements of the pen and to modify its pressure on the paper, are not called upon for strong contraction. It may indeed be the case that they are spared in many instances, but that can only be said to be so after they have been examined by other tests than that of writing.[1]

The muscles of the eyeball were not affected at all, there had never been any diplopia, and I found he was able with promptness and with accuracy to direct his eyes to different objects in rapid succession. In contrast with this I found the levator palpebrae superioris was affected in the same way as the other muscles. Thus when he was directed to look upwards to the ceiling without being allowed to turn the face up as well, and then to look down, it was noticed that the upper lid did not follow the eyeball in its downward movement, so that the sclera was uncovered for about a fourth of an inch above the cornea, and a well-marked furrow remained at the upper part of the movable portion of the eyelid. On repeating this experiment the extent of sclera exposed became less and less until after some eight or ten movements the upper lid moved downwards in perfect harmony with the eyeball as in health. In observing the result of this experiment I was, of course, not unmindful of a possible drag on the upper lid by an unduly retarded relaxation of the frontalis muscle, but no matter how strongly this muscle may act it can have no such effect on the upper lid as to cause the sclera to show between the cornea and its lower edge. Any doubt in one's mind on this point will be set at rest by examination of a patient with third nerve palsy, or with congenital ptosis, for in these affections the wrinkled forehead indicative of sustained effort on the part of the frontalis, though attended with a raising of the brow, is associated with drooping of the upper eyelid. When he was directed to look upwards for some considerable time and then to look downwards, the movement of the eyes was associated with the normal consensual movement of the upper lid. The momentary firm closure of the eyes also immediately restored the normal relationship.

The greatest degree of residual tonicity and stiffness of the muscles was developed by a short but powerful voluntary contraction; after a prolonged contraction, we have seen, the muscles, which of course were firm and hard during the maintenance of the contraction, immediately became soft and natural as in health. On the other hand, it was noticed that movements involving only a very small amount of muscular action did not result in perceptible rigidity; thus it was only when he looked *forcibly* upwards that the sclera was uncovered in the following downward movement of the eye, and the *delicate* handling of a pen or pencil in writing did not cause embarrassing stiffness.

There are many muscles of the striped variety in the body which act sometimes under the direct influence of the will and sometimes, or even usually, quite apart from voluntary effort; indeed I suppose there are few, if any, muscles of which this may not be said. The muscles of ordinary respiration, for instance, which is an automatic process going on without voluntary supervision, may be voluntarily used with greater vigour; the dilators of the nostril which act in synchronism with the inspiratory movement are in many under the control of the will, and such people can dilate their nostrils voluntarily. A muscle which is from certain changes in the nervous system, namely, those involving the proximal motor neurons, incapable of being thrown into action by voluntary

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[1] While this paper is passing through the press I have a letter from Dr. Hale White, who has kindly looked through my manuscript, in which he says that to the very best of his recollection the writing test was not the only one employed in the case of these muscles.

effort, may yet contract in an associated movement ; witness the fact that in hemiplegia the movement of the lower part of the face is sometimes almost natural in smiling, while direct voluntary movement cannot be carried out. An interesting observation was published by C. E. Beevor (3) in connexion with the latissimus dorsi. This muscle, it was pointed out, acts not only under the direct influence of the will, but can be seen to stand out during the short expiratory effort of coughing. Now in a case of hemiplegia it was observed that the former action was almost lost, while the latter was preserved intact. In health, then, it is clear that muscles can be stimulated by the central nervous system through various channels so far as the supranuclear course of the stimulus is concerned, and that in disease some one or other of these channels may be blocked, with results such as I have recounted above.

In connexion with these facts the following experiments were tried : The patient was directed to take very deep breaths so as to call for extra effort on the part of his respiratory muscles, but there was no evidence in embarrassment of the movements of the chest that these muscles became affected by rigidity, though the recti of the abdomen became hard ; there was certainly no rigidity developed in the sterno-mastoids, which were seen to contract during the violent inspiratory act. I then with care observed the behaviour of the latissimus dorsi. When this muscle was thrown into brief but strong contraction by getting the patient forcibly to adduct the arm it became stiff like the other muscles of the body, but when he coughed it was noticed that the contraction associated with this act was not followed by any undue prominence of the muscle. What this means I cannot quite say. I shall have to point out presently that when the muscles were made to contract either as the result of a true reflex, or as is seen in the tendon phenomenon, or by direct percussion, or by means of a single induction shock, no rigidity followed either after single or repeated contractions, and it may be that the short sharp contraction of the latissimus dorsi associated with coughing is allied to these kinds of action of the muscles. When the patient was directed to take very deep breaths while he kept his mouth shut, the nostrils dilated widely as in health during the inspiratory movement, but there was no after-contraction. I then got him voluntarily to expand his nostrils, rather expecting that I might see an after-contraction in this case, but none was observable. So far as it goes this observation is not in harmony with the last, but I record it just as it was noted.

The plantar reflexes were ill marked ; the abdominal, especially the epigastric, were pronounced, and it was noticed that the contraction of the muscles so induced was not followed by any rigidity.

The knee-jerks were well marked, and here again the muscular contraction was not followed by any rigidity.

Idio-muscular contractility was present in the vastus internus, and when this muscle was made to contract by direct percussion I could not satisfy myself that the contraction was slower than usual, or that it subsided more slowly than is normal.

The application of a Faradaic current to the muscles caused a contraction which was followed by stiffening. Remembering the effect of a prolonged as contrasted with a brief voluntary effort, I then applied a strong Faradaic current for a considerable length of time, which kept the muscles in a condition of strong contraction. The current was then cut off, but the same residual contraction was found as after a brief stimulus. Contractions were then caused by subjecting the muscles to single induced shocks, brought about by breaking the primary current. Here the contractions of the muscles, brought about of course through the stimulation of their nerves as in the former case, were not followed by any lasting contraction. The muscles responded to the continuous current with difficulty, and the current had to be strong ; the contractions were followed by spasm as after the interrupted current. I did not think the contractions

of the muscles were more sluggish in their onset than in health, but this was not tested by instrumental means.

Apart from the mere strength of the contraction and its duration, therefore, there are other influences which determine the occurrence or non-occurrence of the myotonic phenomenon, and its intensity when present. It is clear that the mere voluntary or involuntary character of the contraction cannot be accepted as furnishing an explanation. An example has just been given of a voluntary dilatation of the nostrils not being followed by any spasm of the muscles ; on the other hand, it is mentioned by Marie (9) that, in two cases recorded by Weichmann and Westphal respectively, the patients were unable to open the eyes for some short time after sneezing, an act which is eminently involuntary.

I was unable to induce any contraction of the muscles of the forearm by rolling the ulnar nerve under my finger.

The larynx was normal ; the cords came sharply together on phonation and moved readily and widely apart on his immediately thereafter taking a deep breath.

Ophthalmoscopic examination was negative.

The various organs of the body were found normal. When employed in the public-house he took a moderate amount of beer, but was not guilty of any marked excess. There was no history of venereal disease.

Family History. The mother of the patient was a remarkably intelligent old woman of 72, who told me that her mother died at the age of 77 from causes unknown to her ; sudden death, also from unknown causes, overtook her father at the age of 60. Her brothers and sisters were healthy and free from the ' family stiffness ', as she termed the affection. She had had 9 children, of whom 6 were dead—3 sons, who died respectively in infancy and at the ages of 34 and 36, and 3 daughters, two of whom died at the age of 5 weeks, and one at the age of 4 years. Of the 3 living children I have already recorded the case of one ; a second is the Mrs. G. whose case is referred to below ; while the third, a daughter, is married and has children, all of whom are free from the disease. The only two instances of the affection occurring in her children were those of S. and Mrs. G.

During the time she was pregnant with her last child, who was the patient S., and at a time, therefore, when she was 38 years of age, she became affected with the family stiffness. This, she says, came on quite early in the pregnancy, as soon indeed as she knew that she was pregnant, and continued throughout its course, ceasing on delivery and not making its appearance again. Her hands were not affected, but she noticed the symptoms mainly in her legs. She used to ' stick ', as she described it, on making the initial effort in going upstairs, and then go up easily. The account which this intelligent old woman gave me of her symptoms left me in no doubt but that she had had a milder manifestation of the same disease.

She stated that all her children began to walk at an early age, that Mrs. G. was affected in early childhood, and that in the case of S. she detected the disease at an earlier age than she otherwise would have done, probably because she was then familiar with its features, and, as she said, because she feared its development, having had the symptoms herself during the pregnancy.

I had an opportunity of examining Mrs. G., the other member of the family who was affected. She was 42 years of age, had been married nineteen years, and had had eight pregnancies, the first, third, and fourth resulting in dead-born children ; of those born alive, one, a girl, was 15 years old, and I satisfied myself that she was free from the disease, while four had died in early childhood from some kind of convulsive attacks.

Mrs. G. had good general health. She had had the stiffness as long as she could remember. When she was a child she could not play with the other children ; she was easily knocked over, and used to notice that when the class

was dismissed she was always last out of the room, and that all the others got out before she could make a proper start. She never could skip, but could only perform the humbler duty of turning the rope for others.

She mentioned instances of the way in which she had been affected. On one occasion, some years previously, she was hesitating whether to attempt to cross the street or not as a van was coming along ; she decided that she might risk it and made the attempt : she tripped and fell on her face and, though unhurt, was unable to rise for some seconds, nearly getting run over in consequence. She said that all her muscles had been at times and in turns affected, and that the symptoms had varied considerably in severity. From the date of her first pregnancy she had begun to improve, and whereas at one time she was quite unable to work, she was now able to earn her living. The manner of this improvement had been remarkable, for each succeeding pregnancy was associated with a return of more marked symptoms, but after delivery the lost ground was more than made up. The course of the affection had never been influenced by menstruation, which had always been normal.

At the time of my examination she was making her living by working at a woollen mill, and stated that she was always very careful to keep out of the way of the driving band, well knowing that a slight slip might, with the condition of her muscles, put her in danger from which she could not extricate herself. At one stage of the work all the operatives had to run upstairs, and this happened frequently during the day ; on these occasions she always made as early a start as she could, stuck at the second or third step, and was always outstripped by the others, who started after she did.

She said that her speech was sometimes interfered with by her tongue sticking in her mouth, but this was strenuously denied by her husband, who was convinced that in this respect there was no incapacity !

When I examined her there was no doubt as to the diagnosis, for when she forcibly closed her hand she developed the characteristic stiffness in the muscles, so well shown by her brother, which made it impossible for the hand to be opened at once. This symptom was, she assured me, not constant in severity and was sometimes absent. The few tests which I applied seemed to indicate that the other muscles were free from the affection, but she stated that even then she used occasionally to 'stick' in beginning to go upstairs. She moved her eyes with precision, but said that sometimes she had a difficulty in opening them. Her power of swallowing was normal.

Sequel. I have recently had the opportunity of following up the history of this family and of examining S. and Mrs. G. The mother died about six years ago, not having had any return of the symptoms.

Mrs. G. is now entirely free from any manifestation of the condition. She dates the complete cessation of the symptoms from Christmas, 1909. Her daughter, now in her twenty-fifth year, remains unaffected.

S. expresses himself as being very much better. Acting on my strong advice and influenced by his own experience, he decided to lead an active life and make the best of matters, and he has manfully done so. During the last nine years he has been employed in a warehouse in a capacity in which he has a good deal of walking about and a certain amount of writing to do. No one in the warehouse knows of his disability ; he can do the work quite satisfactorily and, as he says, concealment has now become an instinct with him. On careful examination I cannot satisfy myself that there is any material improvement in the condition of the muscles, and all the phenomena described above are still well marked. The muscles are still well developed and none of them show any signs of atrophy. His general health remains excellent. He had an attack of herpes frontalis in 1909, of which the scars are seen.

II. Myotonia Atrophica et Hypertrophica.

E. H. came under my observation for the first time towards the end of 1909, and since then he has been admitted into the Infirmary on several occasions. My last full examination of the patient was made on June 29, 1911, and the description to be given is based on what was then found.

The patient was a man of 48 years of age. His face was of the myopathic type and had a singularly vacant expression which varied very little. There was clearly some loss of power of the muscles of the face; he could not close his eyes completely, the lids remaining about a fifth of an inch apart. When he tried to elevate his eyebrows there was very little wrinkling of the forehead. He could not whistle, and the orbicularis oris and the buccinators were demonstrably weak. When he was directed to make slight grimaces it was interesting to see how these persisted for some time after the effort to produce them had passed off. So far as could be made out the slight variations in expression which were developed by emotions were rather lasting in character. It was interesting to note, especially in connexion with what follows, that the eyelids separated at once to their normal extent on the cessation of the effort to close the eyes. When he made any kind of muscular effort, even if that consisted merely in the elevation of one arm, the expression of his face at once altered; one or two vertical furrows appeared towards the middle of the forehead and a staring expression of the eyes was found to develop. If he made a supreme effort, such as trying to raise himself to the sitting posture in bed without the use of his arms, the changes became much more marked; the vertical furrows became very deep, the upper eyelids became spasmodically retracted and the sclerotics largely uncovered, and when the effort passed off the expression developed and the retraction of the upper lids remained for some time, gradually disappearing in about three-quarters of a minute.

He could follow a moving object with his eyes rapidly and with perfect precision in any direction; varied movements could be carried out in rapid succession, and it was clear that the muscles of the globe were not affected. He stated, however, that during the last eighteen months he had occasionally had double vision.

When he looked forcibly upwards there was prompt and full elevation of the upper lid, with the development of a well-marked furrow at its upper part as in the normal condition. When he then at once looked downwards the upper lid remained retracted so that the sclerotic coat of the eye was largely exposed above the cornea. The frequent repetition of these movements caused the phenomenon to pass off and there was normal consensual downward movement of the upper lid. When he was directed to look up forcibly and to maintain his upward gaze for some considerable time it was found that when he then looked downwards the upper lid followed the movement of the eye as in the normal condition. When he looked forcibly upwards and then immediately attempted to close the eyes he succeeded as well as was usual in his case; the furrow at the upper part of the eyelid at once disappeared, from which one must conclude that the residual contraction of the levator palpebrae superioris could be at once overcome by the orbicularis, weak though that muscle was; and it was also found that the attempt to close the eyes at once restored the normal relationship between the downward movement of the eyes and that of the lids, so that when he looked down the sclerotics were not exposed above the corneae.

He had difficulty in mastication, especially, he said, in dealing with the first few mouthfuls. The muscles of mastication were very weak. The contraction of the temporals, masseters, and internal pterygoids, which were of course accessible to direct palpation, was weak and in each case the relaxation was slow. It was clear

that the external pterygoids were profoundly affected; his greatest effort to open the mouth resulted in a separation of the incisor teeth of not more than three-quarters of an inch; in this movement the chin moved backwards and the condyle of the jaw did not leave the glenoid fossa and mount the eminentia articularis of the temporal bone as it does normally. The attitude of the patient's jaw can be accurately imitated by any one who opens his mouth as wide as he can without allowing his condyle to leave the glenoid cavity.

There was some difficulty in swallowing, but this was variable and inconstant. Sometimes the food seemed to stick 'about half-way down his neck', and great efforts at swallowing were without effect, so that the patient found it wise to flex the neck and push the food back into the mouth by pressing with his thumb below the point of obstruction.

The tongue could not be protruded much beyond the teeth nor freely moved from side to side. It felt flabby and it could not be voluntarily hardened.

His speech was slow and indistinct, with a tendency to slurring of the words. He said he sometimes found himself quite unable to speak for some minutes, and attributed this to a feeling of tightness in the floor of the mouth. At one time he had a strong voice; now he could not raise it, and he certainly could not shout, his voice being inaudible at a distance of twelve feet, though one could see he was making a great effort.

On examination with the laryngoscope the cords were found in the cadaveric position. On placid respiration there was very little movement. On full inspiration they were approximated to a slight extent instead of moving asunder as in health, the ingress of air being apparently more than enough to neutralize the feeble abducting power which remained. On phonation the cords came together, but neither tightly nor promptly. What little muscular power remained appeared to be confined to the left side.

There was extreme wasting of both sterno-mastoids, the only indication of the existence of the muscle being at the anterior and lower part where the tendon of origin from the sternum could be made out. It was very striking to be able to put one's finger over the inner part of the clavicle without meeting any resistance from the existence of this muscle. When he looked over his shoulder the loss of the normal contour of the opposite side of the neck was emphasized; instead of the firm pillar of the sterno-mastoid there was a uniform concavity in which one could see with great facility the pulsations of the internal jugular and sub-clavian veins, and where the anterior aspect of the spinal column was singularly accessible to palpation immediately to the outer side of the larynx and trachea. In consequence of this wasting of the sterno-mastoids he was unable to lift his head off the pillow, though during the attempt to carry out this movement what little sterno-mastoid he had was demonstrated; one could see the platysma stand out prominently, and it was found that both muscles remained contracted for some time after the head fell back on the pillow. The scalene muscles, which could be readily felt, remained contracted for some time after the effort which called them into play had passed.

There was no wasting of the trapezii, serrati, pectorals, deltoids, or other muscles of the shoulder or of the upper arm.

When at rest the elbows and wrists were slightly flexed, but not unnaturally so, and the forearms were in a condition of pronation. The metacarpo-phalangeal joints were very slightly flexed, but not more so than in many a normal hand when at rest. The phalangeal joints were all extended, the first inclining towards hyperextension. The thumbs, flexed at their metacarpo-phalangeal and extended at their interphalangeal articulations, lay well in front of the palm, so that they were almost out of sight when the hand was looked at from behind. The first impression conveyed to one's mind was that the attitude of the hand was due to spasm, but examination showed that if the limbs were carefully handled there was no true spasm, care being taken to exclude voluntary movement on the part

of the patient.   There was much wasting of the muscles on the back of the fore-arm with well-marked wrist-drop, and efforts to extend the wrist were almost without result, but it was noticed that the muscles on the back of the forearm contracted slightly during these efforts and remain contracted for some time after-wards.   When he was directed to clench his hand firmly there was an increase in the flexion of the wrist, the grasp was very imperfectly made, and as the terminal phalanges were not flexed the nails remained visible.   The effort was associated with a general contraction followed by a stiffening of all the muscles of the forearm.   As the result of very numerous observations I came to the conclusion that the most rapid relaxation of the muscles was obtained by a simple cessation of effort on his part.   So long as he persevered in efforts to open his hand and extend his fingers the general rigidity of the muscles of the fore-arm seemed to persist, and it was only after very repeated attempts at opening and shutting the hand that I could satisfy myself that the rigidity became less. When he kept up the effort of trying to clench his hand as firmly as possible for a considerable time and then tried to open it, the stiffness was found to be much less than after a momentary effort of the same kind.   The muscles of the upper arm, the pectorals, and the trapezii all showed the myotonic condition.

The lower limbs were well developed and the calves were exceptionally large, measuring $14\frac{1}{2}$ inches in circumference.   There was very little subcutaneous fat in the legs and the skin was freely movable on the deeper parts.   The strength of the muscles was impaired and he could not keep the extended limb raised from the bed for any length of time.   In the calves the outlines of the muscles could be readily recognized, and, especially on the left side, the lower fibres of the soleus were unusually manifest.   As he lay in bed the ankle-joints were always found in a condition of plantar flexion, the arch of the foot pronounced, the metatarso-phalangeal joints dorsiflexed and the interphalangeal in a state of slight plantar flexion which was less marked in the case of the great toe.   Here again the appearance of the limbs was suggestive of spasm, but on palpation the muscles were not found to be tonically contracted.   Passive dorsal flexion of the ankle-joint could not be carried beyond a right angle, and when it was carried as far as this the muscles of the calf were made hard from tension.   Some shrinking in length of the muscles of the calf appeared to be present, and to this I attributed the slight degree of prominence of the tendo Achillis which was present even when the limb was at rest.

He had difficulty in dorsiflexing the ankle-joints, and the movement was carried out slowly.   Inversion and eversion of the foot were similarly impaired, and perhaps the tibialis anticus was the muscle whose action was most affected. He could move his toes with a moderate degree of freedom.   The tendons on the dorsum of the feet stood out during these efforts and remained prominent for some time after the effort had ceased, the bellies of the corresponding muscles also remaining contracted.   Vigorous attempts at plantar flexion of the foot against resistance (and in this action the muscles of the calves were found to be pretty strong) were followed by a lasting contraction of the gastrocnemius and soleus muscles.

The muscles of the thighs showed the same peculiarities in their action, but in a much less pronounced degree.   In the muscles of the abdominal wall they were well marked.

The knee-jerks were well marked on both sides; the contraction was momentary and passed off at once.   There was no patellar clonus and no ankle clonus.   There were no tendon-jerks to be made out in the upper limbs.

Direct percussion over the vastus internus caused a contraction of the muscle similar to that normally found.   It did not appear to be sluggish in onset or of longer duration than is normal.

The plantar reflexes were flexor in type.   The cremasteric and abdominal reflexes were present.   The pupils reacted to light and with active accommodation.

He described peculiar attacks to which he was subject. These varied much in frequency, and during his fourth stay in the Infirmary they came on as a rule every day. He said the attack was preceded by an indescribable sensation in the lower part of the back, which passed upwards and caused the muscles to contract. The arms were shot out from the side and the legs were extended. The condition lasted a few seconds, was not associated with any mental confusion, and left no after-effects.

He could stand in a natural position, and even with his feet close together and with his eyes shut he could stand without much swaying. There was no undue lordosis, nor was there any excurvation of the spine when he sat on a chair. When he walked he raised his feet unduly and brought the toes to the ground first, so that the soles of his feet were very plainly visible from behind. When told to lie down on the floor he carefully got down on one knee with his hand on the edge of the bed for support, then on the other knee, and then upon all fours, from which position he rolled round sideways on to his back. When he got up from this position he turned on to his hands and knees, and from this attitude he either got up in a manner resembling that of ordinary cases of pseudo-hypertrophic palsy, but without the marked hanging down of the head which is so common, or he managed to get up without the instinctive precaution of extending the knee-joints before putting the weight of the body on them.

On testing the muscles with the Faradaic current the anterior tibial group in the legs and the extensor group in the forearm reacted feebly; those of the calves and the flexor muscles of the forearm reacted much more readily. In all the muscles examined it was noticed that the contraction induced remained for some few seconds after the cessation of the current. When a strong Faradaic current was applied to the forearm and kept on for a long time the contraction of the muscles remained for some time after the terminals were removed, but I think this was less marked than after a brief application. When the muscles were made to contract by a single induced shock, developed by opening the primary current (for with the strength employed no reaction followed the induced shock developed by *closing* the primary current), the contraction was purely momentary and no trace of abiding contraction could be made out by the unaided senses.

With the galvanic current the closing contractions were greater than the opening, which latter, especially the anodal, were almost invisible. The anodal and cathodal closing contractions were about equal. Some residual contraction was apparent after each time the muscles were made to respond.

The patient was a man of good intelligence and did not strike me as being neurotic or in any way peculiar. He said his memory was uncertain, and from time to time he has supplemented the information he gave me by long letters written after consultation with his wife as to the sequence of events. For a man in his position he wrote a good hand. He took some time to fix the pencil or pen, for he could use either, in its proper position, and used the left hand to place the fingers of the right in their suitable relationship to the instrument he used for writing. He had more difficulty with the first few words than with those which followed.

There was no affection of ordinary tactile sensation, and he was quite clear as to the difference between heat and cold. Taste, smell, and hearing were normal. Ophthalmoscopic examination was negative.

The various organs of the body were healthy. I did not associate the abnormal cardiac signs with the presence of organic disease in that organ. The pulse was usually infrequent; on his first stay in the Infirmary it was usually below 60, and on one occasion fell to 48; on the second occasion it was very often below 50, and on some occasions fell to 40, but towards the end of his stay it was above 50 or 60 or even higher; on the third occasion it sometimes fell to 40, was more usually in the fifties, reached 92 one day, and often varied between 60 and 80. During

his fourth stay it varied from 48 to 80, being usually in the fifties.   When under my observation lately I have always found the pulse very infrequent, and I have counted it as low as 36.

At no time was there any heart-block.   Extra-systoles were frequent during all the time he was under my observation, but the infrequency of the pulse above noted was independent of these.   The extra-systoles were mostly of the ventricular variety ;   some were possibly auriculo-ventricular in origin.   On one occasion an intercalated ventricular extra-systole was made out.

The temperature was almost invariably subnormal.

The patient had eight children living, varying in age from 20 to 3 years. He had lost five.

There was no history of venereal infection and he had been moderate in the use of alcohol.

The manner of onset of the symptoms in this case, and their progress, are of interest.   Until the age of about 26 the patient had excellent health and was an ardent football player.   In 1891 he had an attack of ' rheumatism ', following which he was off work for four or five months with vomiting and diarrhoea. These abdominal symptoms recurred several times in the next few months.   He then resumed work and continued working for nine or ten years.   In 1900 he had a second attack of ' rheumatism ', and was off work twelve weeks.   In 1901 he had ' pleurisy ' ;   he was at home three or four months, had stabbing pains in the axillae and, it is interesting to note, heard his doctor comment at this time on the slowness of his pulse.   During the greater part of 1902 he was off work with swelling of the joints of the arms and legs and generalized pains, and in 1904 the symptoms referable to ' pleurisy ' again came on.   In 1905 he had symptoms referable to the heart, and manifestly of the kind complained of by those who are the subjects of extra-systoles.   About this time he began to have ' creepy feelings and attacks of shaking ', with some stiffness of the neck.

One morning in February, 1906, his wife was awakened by his making a strange noise in his throat.   He was perfectly conscious, but felt unable to speak, as his mouth was closed and he could not open it.   He also thinks his mouth was drawn to the left side.   The right hand was firmly clenched and neither he nor his wife could open it, and he had lost the use of his right leg. The clenched condition of the hand passed off gradually.   On getting up the following morning he found the right leg stiff and somewhat bent at the knee. His mouth remained drawn to the left and so closed that he had difficulty in talking or feeding himself.   The face and leg got rapidly well, but the arm remained weak.   In a fortnight he went back to work, and at the end of a few days his left hand became affected in the same way but not to the same extent.

He was admitted into the General Infirmary at Leeds for the first time on July 25, 1906.   Dr. Barrs, under whose care he was admitted, was away on holiday during his stay in hospital, so we are without the assistance of his opinion as to the condition at this time.   The speech was noticed to be slightly impeded, but there was no aphasia.   His grip was poor, especially on the right side, and supination was impaired.   He said that he could move his arms a short distance, but that then twitching began and he could move them no further ;   this was more marked on the right side.   His expression was dull and vacant.   There was some wasting of the muscles of the forearms, with marked weakness of the extensors ;   the hands were kept in a constant attitude, the wrists being flexed, as were also the metacarpo-phalangeal joints, while the inter-phalangeal joints were extended.   There was some rigidity of the elbow-joints. The triceps and supinator reflexes were not made out.   Both knee-jerks were brisk.   He walked with his feet well apart, and some rigidity of the knees was noted.   The cardiac action was irregular and tended towards infrequency.   Some improvement took place during his stay in the Infirmary.   On admission he

was unable to feed himself, but on his discharge he was independent in this respect.

The patient was admitted under my care for the first time in September, 1909. He was twice in the Infirmary during 1910, and was again admitted on June 27, 1911, when the condition was as described above. Since I saw the patient first there had been a steady increase in the symptoms. It was some time before I grasped that he was affected with the essential symptom of myotonia. The attitude of the hand and fingers and the fact that a certain amount of spasm was always assertive in the absence of precautions to eliminate all voluntary movement (and these precautions I had not taken), together with the briskness of the knee-jerks, led me to think there was some lesion of the upper motor neurons. The expressionless appearance of the face and the inability to protrude the tongue were attributed, as were the sterno-mastoid and laryngeal palsy, to an affection of the nuclei of origin of the nerves, and I inclined to a diagnosis of amyotrophic lateral sclerosis. The marked enlargement of the calves and the limitation of passive dorsal flexion of the ankle-joint, with a peculiar hardening of the gastrocnemius and soleus muscles when this was attempted, suggested a resemblance to pseudo-hypertrophic. muscular palsy ; and these symptoms, together with the lack of consensual downward movement of the upper eyelid, led to a reconsideration of the diagnosis. It was not till November, 1910, that I fully grasped that he was the subject of myotonia, though I have not the least doubt that the symptom was present from the time he first came under my observation.

There is no doubt that the weakness both of the arms and legs had increased markedly since I first saw him, that his face was much more wanting in expression, and that the laryngeal palsy had become more pronounced.

The patient readily assented to the removal of small portions of muscle for histological examination. This was done by Mr. A. Richardson, our resident casualty officer, under local anaesthesia induced by cocaine and adrenaline. Care was taken to avoid the injection of any of the fluid into the muscular fibres. The proceeding was quite unattended with pain. Portions of the inner head of the gastrocnemius and of the extensor carpi ulnaris were selected. When the small area of the muscle from which it had been decided to remove the portion for examination had been exposed, the opportunity was taken to get the patient to execute a voluntary contraction involving the muscle in question. It was striking to see the muscle swell up and project at the wound, and then, when the effort was suspended, remain contracted for some considerable time. This was more marked in the case of the leg than in that of the arm.

The portions of muscle removed were handed to Mr. Matthew J. Stewart, the director of our pathological laboratory, to whom I am much indebted for the following report :—

Histological examination. The portions of muscle removed show quite definite deviations from the normal appearance. By way of control, portions of muscle were taken immediately after death from corresponding situations in a case in which the structure was presumably normal. All the material was fixed in formalin, and, after embedding in paraffin, sections were taken both horizontally and longitudinally.

The changes present varied somewhat in the two limbs, upper and lower, but in each instance they may be classified as variations in size and in shape of the fibres, and variations in the number and distribution of the nuclei.

1. In both the arm and the leg the muscle fibres, as measured by the micrometer, varied from 30 to 120 μ in diameter, but the great majority fell

between 60 and 90 μ.   In the normal control muscle most of the fibres measured from 25 to 50 μ.   Thus in the diseased muscles the fibres were, roughly speaking, twice the diameter of those in the control.

2. In transverse sections of the control arm and leg muscles, the fibres were markedly polyhedral in shape from mutual pressure, even where they had been separated in manipulation.   In the muscle from the affected forearm the fibres, as seen in transverse section, were almost circular.   In the case of the leg this change was much less marked, though some loss of the normal polyhedral outline was beyond doubt.

3. In both the arm and the leg there appeared to be very marked nuclear proliferation within the muscle fibres.   An attempt to estimate the precise extent of this change was made by counting the number of nuclei seen in transverse sections.   Only nuclei attached to, or actually within, the sarcolemma were taken into account, and only such fibres as appeared to be cut exactly transversely.   Since all the sections were cut approximately of the same thickness, any error arising from inequality of thickness is probably small.

The results may be tabulated as follows :—

	Nuclei per muscle fibre as seen in T. S.
Affected forearm	6·65
Normal forearm	1·95
Affected leg	4·4
Normal leg	2·4

There were thus in the case of the forearm roughly three times as many nuclei per fibre as is normal, and in the case of the leg about twice as many.

A striking feature in the case of the forearm muscle was a great increase of nuclei *within* the fibre.   This change was not found in the muscle of the leg.

Another change which was best marked in the leg, and was made out in the longitudinal sections, was a tendency in some of the fibres for the ultimate fibrils to assume a wavy appearance, and this was sometimes associated with irregularity in outline of the whole fibre.   In these fibres the transverse striation was less marked than in the others.   Apart from this change there are none which can be attributed to degeneration of the muscle, nor is there any increase of interstitial tissue, either fibrous or fatty.   Examination of sections stained with pyronin-methyl-green failed to show the presence of any abnormal cellular elements.

PROGNOSIS IN THOMSEN'S DISEASE.

It is not surprising that the prognosis of a disease at once so rare and so chronic in its course should be differently stated by different writers.   Hale White (16), writing in 1886, says the affection ' may pass off'.   In his article in the *Guy's Hospital Reports* he says, ' Probably in no genuine case of Thomsen's disease has this stiffness passed off' ; and again, ' It is almost certain that the

disease does not get well; anyhow, if it does, the recovery is extremely slow.' He is even more pessimistic in 1910, for in his article in *Allbutt and Rolleston's System* he writes, 'So far as it is known the disease never passes off.'

Herschell gave an account of two examples of the disease at a meeting of the Medical Society (7), and in his reply on the discussion stated that a sister of the patients had had the disease, but 'got quite well after marriage'. He did not mention whether this recovery followed on pregnancy.

Gowers and Taylor (6), writing in 1899, say, 'Once developed, the condition seems to persist, with little change, through life,' and they guardedly remark, 'It is possible that the influence of therapeutics is not yet exhausted.'

There are some considerations, however, which enable one to take a more favourable view, and among these are the following: Gowers and Taylor state, on the authority of Thomsen, that a life of active muscular exertion does most to ameliorate the condition, and this is an observation which has been confirmed by others. In the case recorded by Ballet and Marie the muscles of the eye were affected by the myotonic condition, but this passed off at the age of 24. In other instances the affection has apparently been transient. Again, the severity of the symptoms is well known to vary, apparently under such influences as heat and cold, fasting and repletion, fatigue and, according to some, emotion. Pregnancy seems to have some influence in lessening the symptoms.

It is indeed true that all recent observations show that in this disease the muscular fibres are enlarged, but this does not commit one to the view that the peculiarity in the behaviour of the muscles is altogether dependent on this structural anomaly. The observations of Ringer and Sainsbury (11), quoted by Hale White, show that muscles may be made to contract in the same way as is seen in Thomsen's disease, under the influence of phosphate of soda; and veratria is credited with the same effect. It is possible, therefore, that some contributing cause is necessary for the appearance of the symptoms. On the other hand, Gowers and Taylor, in the chapter dealing with muscular hypertrophy, after commenting on the difficulty of determining by microscopical examination whether muscular fibres are or are not truly hypertrophied, quote Auerbach and Eulenberg as having recorded cases in which the muscles, though weakened in their action, were enlarged and firm to the touch, and in which the fibres were greatly increased in diameter and the nuclei augmented in number, without there being any increase in the interstitial tissue. The condition of the muscles on histological examination was therefore very similar to that found in my patient (E. H.) and that found in other cases, and yet there was no myotonia.

These considerations, suggesting as they do that myotonia is not altogether due to alteration in the structure of the muscles, encourage me to think that if the history of the cases of myotonia which have been recorded could be followed up, the experience which has fallen to me of seeing two cases which have completely cleared up might not prove to be so very exceptional.

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DESCRIPTION OF PLATES.

PLATE 9.   (Case of S. C.)

FIG. 1. The patient was directed to look forcibly upwards and then at once to look downwards. The photograph was then taken, but without undue haste, as the eyelids remained in the position shown for some time.

FIG. 2. This photograph was taken after the patient had looked upwards and downwards about nine or ten times.

The undue exposure of the sclerotic coat is well seen in Fig. 1. The furrow at the upper part of the movable portion of the eyelid is also pronounced. In each case the patient's downward look was regulated by his directing his eyes to a chalk-mark on the support of the camera.

FIG. 3. He was directed to clench his hand firmly and then at once to try to open it. The photograph was taken with a shutter exposure at an early stage in the effort of opening. The forefinger is just beginning to unbend and the thumb has lost the flexion of the terminal joint which is found in a closed fist.

FIG. 4. This was taken under the same conditions as Fig. 3, but on a different occasion and, as may be seen, at a later stage of the effort to open the hand.

PLATE 10.   (Case of E. H.)

FIG. 1. Full-length photograph. Shows the attitude of the hands, the wasting of the forearms, and the great enlargement of the calves.

FIG. 2. Back view. Shows the good development of the muscles of the shoulder, the absence of any evidence of serratus palsy, and the wrist-drop. The flexion of the elbows is voluntary.

PLATE 11.   (Case of E. H.)

FIG. 1 *a*. Right upper limb held out by the patient without his making any further effort. The wrist-drop is well marked.   Any attempt on the patient's part to extend the wrist fails to produce this result, but causes spasm of the muscles and some increase of the flexion of the wrist.

FIG. 1 *b*. He was directed to try to clench his hand firmly and then at once to try to open it.   The photograph was taken about 2 or 3 seconds after the beginning of this attempt to open the hand.   The flexion of the wrist and of the metacarpo-phalangeal joints is seen to have increased, the thumb is more turned towards the palm, and the tendon of the palmaris longus stands out prominently.   During the taking of this second photograph the arm of the patient was prevented from being accidentally removed from the field of the camera by an assistant, whose hand is seen steadying it.

FIG. 2 *a*. Taken when the patient was sitting at rest.   The sterno-mastoid muscles are almost invisible.

FIG. 2 *b*. The chair on which the patient was sitting was then tilted backwards to an angle of about 45 degrees with the floor, and the patient was asked to make a strong effort to sit up.   He did not succeed in sitting up, and at the end of about 3 seconds he was directed to discontinue his efforts.   At the same moment the chair was put back into its former position, and in about 2 seconds thereafter the photograph was taken.   There are well-marked vertical furrows towards the middle of the forehead, with some drawing down of the brows, due to the action of the corrugator supercilii.   In spite of this drawing down of the brows the eyes are more widely open and staring in expression.   The sterno-mastoid tendon is visible and some fasciculi of the platysma myoides can be seen.   It took about three-quarters of a minute for this expression of effort to pass off.

PLATE 12.   (Case of E. H.)

FIG. 1. The patient was directed to look up forcibly and then at once to look downwards. The photograph was at once taken.   It is seen that the upper lid has not come down with the eye as it normally does.   The furrow at the upper part of the movable portion of the eyelid is well marked.

FIG. 2. He was then directed to look forcibly upwards and downwards repeatedly.   At each movement of the eye downward, there was noticed a progressive improvement in the amount of the normal consensual downward movement of the upper lid.   The photograph was taken after he had carried out about a dozen of these upward and downward movements.   It is unfortunate that in this second photograph the patient is not looking quite so much down as in the first, but it is clear that the spasm of the levator palpebrae superioris has quite passed off.

PLATE 13.   (Case of E. H.)

FIGS. 1 and 2.   Transverse sections, respectively, of affected forearm (Fig. 1), and of the corresponding muscle from a healthy limb (Fig. 2).   These show (1) the increase in the size of the muscle fibres in the affected limb; (2) the rounded character of the fibres in contrast with the normal polyhedral form; (3) the increase in the number of muscle nuclei.   (The last point is not well brought out in the microphotograph.)   × 60.

FIG. 3. Longitudinal section of gastrocnemius, showing the peculiar wavy appearance presented by some of the muscle fibres.   The increase in the number of nuclei is well seen.   × 120.
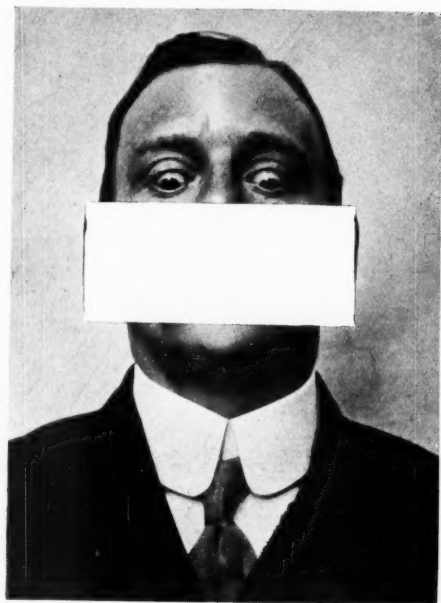
FIG. 1

FIG. 2

FIG. 3

FIG. 4
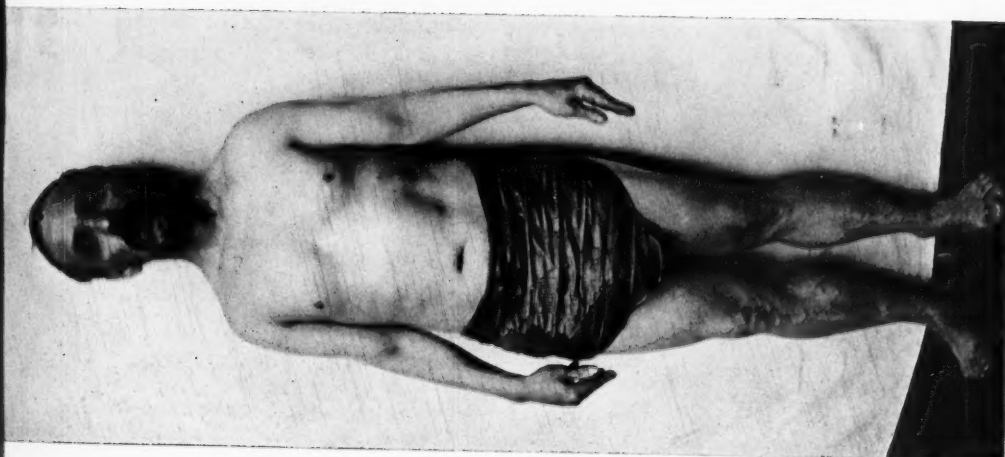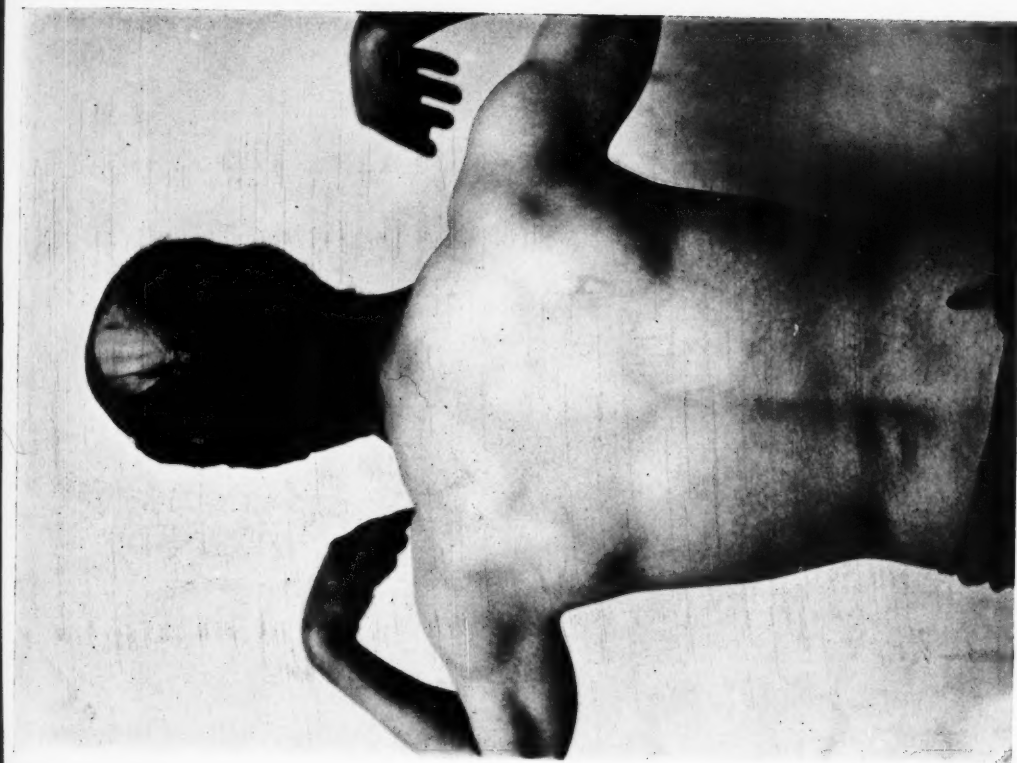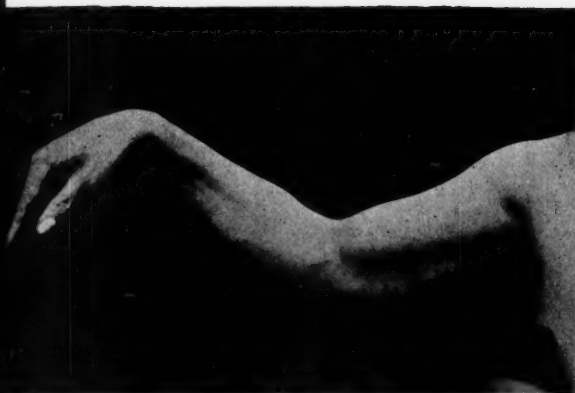
Fig. 2

Fig. 1

FIG. 1 a

FIG. 1 b
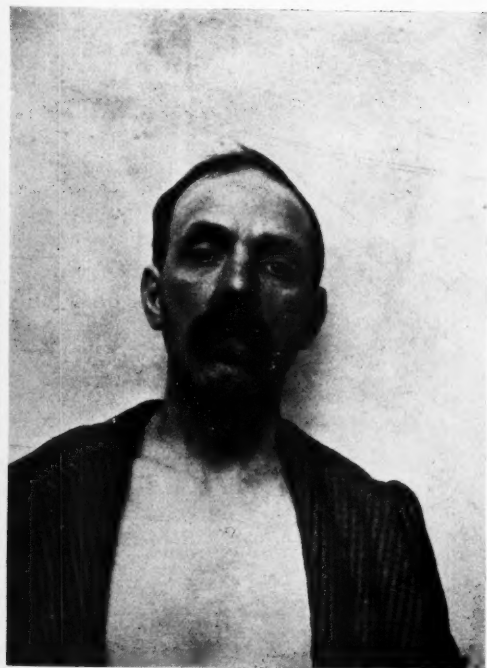
FIG. 2 a

FIG. 2 b

Fig. 1
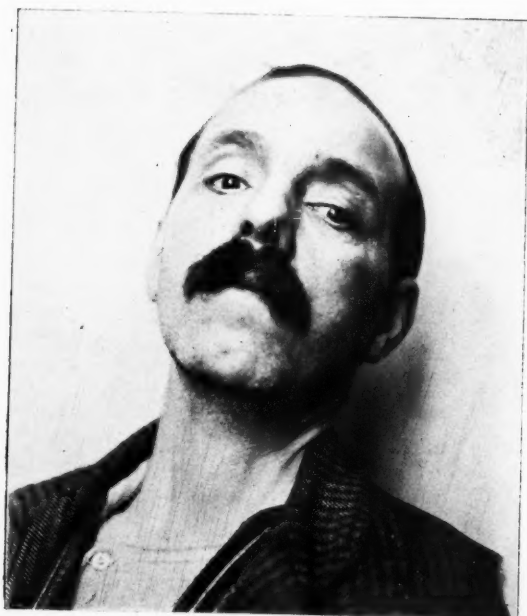
Fig. 2

FIG. 1

FIG. 2

FIG. 3

THE DISTRIBUTION AND EXCRETION OF RADIUM AND ITS EMANATION AFTER INTERNAL ADMINISTRATION

By E. BELLINGHAM SMITH

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With Plate 14

BUT little work has been done in regard to the internal administration and excretion of radium and its derivatives; and that which has appeared has failed to deal quantitatively with the subject.

It is proposed, therefore, in this paper to consider the actual distribution and fate of radium and its derivatives after their introduction into the body.

Method. The most convenient way of estimating the activity of radium is by means of the electroscope. In the experiments which have been undertaken two different types have been used.

The first is the a-ray electroscope. This instrument gives only an approximate value and is not applicable to those substances which emit emanation. Its use is restricted to finding the available a-ray activity of a given specimen and cannot be applied to determine the total radium content, as the rays employed only proceed from a superficial layer. In dealing with the emanation, and also in practically all estimations requiring a quantitative and accurate result, the emanation electroscope has been utilized. In this instrument the quantity of radio-active material present is gauged by the measurement of the emanation in equilibrium with it.

Distribution and Excretion of Radium.

We will first of all consider the fate of a pure radium salt after its administration by the mouth. In this case only one experiment was performed on account of the costliness of the material.

For the experiment $\frac{1}{22}$ mg. of pure radium bromide was dissolved in 2 c.c. of water; to this solution was added a very small quantity of bread. A mouse was then placed by itself in a cage at 12.45 p.m. on July 14, with no other food than the radio-active sop. At the end of $4\frac{1}{2}$ hours the sop had all disappeared. A very small quantity of fresh sop was then placed in the bowl, so as to avoid any loss of radium; this was eaten by 5.30 p.m. of July 14. The animal was then killed.

The stomach, small intestine, and large intestine were each separately tied off and placed in different vessels. The other viscera were treated in the same way and sealed up. Each separate portion of the gastro-intestinal tract was then

carefully washed in normal saline until as far as possible free from any contents.

One month later an estimation of the activity of the various organs was commenced by means of the emanation electroscope. The viscera were finely minced in water, heated in separate flasks, and the products collected and drawn in turn into the emanation electroscope. An examination was made in this way and the maximum leak in each case recorded. The table below shows the various organs examined, their respective weights, and the activity of each in scale divisions per minute. In the final column the activity in scale divisions per gramme of tissue is given :—

Organs.	Weight in grm.	Activity after second estimation in divisions per min.	Activity in scale divisions per grm.
Kidneys . . .	0·418	562	1340
Liver . . .	1·780	138	78
Stomach . . .	0·191	44	230
Small Intestine . .	1·352	214	150
Large Intestine . .	0·559	327	580
Lungs	0·534	75	140
Muscles ⎫ Bones ⎬ . . . Skin ⎭	24·400	1529	62
Intestinal contents .	Not weighed	Too great an activity for accurate estimation. *circ.* 6000 divisions per min.	
Quantity left after feeding	,,	804	

From this we see that the greatest activity lies in the kidney, while that of the large intestine occupies the second place. We shall discuss these figures later when dealing with the estimation of the radio-activity of various organs after injection.

It would not seem reasonable to expect any absorption to occur after the administration of the insoluble salts of radium by the mouth, but as they have been given as a therapeutic agent, it is necessary to settle this point definitely.

Experiment. Three full-grown mice were given 30 mg. of 250 radium barium sulphate daily for three consecutive days. On the evening of the third day two of these mice were separated and placed in a cage specially adapted for the collection of their urine and faeces. The accumulated faeces and urine passed during the subsequent seventeen hours were then taken and examined separately in the emanation electroscope as described above. The urine failed to show any activity. The faeces, on the other hand, were markedly active. Radio-active material was therefore being consumed and excreted by the two mice under observation. A fourth dose of 30 mg. was then given and a similar examination yielded a like result; faeces active, urine not.

A fourth mouse was now taken and the administration of radium barium sulphate was continued with the third mouse of the other experiments. During the following twenty-seven days 210 mg. of 250 salt were given by the mouth. On three separate occasions the urine and faeces were collected for periods of

twenty-four hours and examined. The activity of the faeces was marked, while none existed in the urine.

On the twenty-seventh day both animals were killed ; the whole gastro-intestinal tract was carefully ligatured and removed ; the other viscera were then treated in the same way.

The organs selected for examination were the kidneys, liver, and spleen. All these viscera showed a slight temporary activity, which, however, disappeared after a few hours, and was probably due to a trace of circulating emanation and not to radium. This estimation was made with the a-ray electroscope. The bowels were then taken and carefully freed from their contents, and both were saved. An examination was then made of the bowel and contents respectively. It was found that while there was marked activity in the intestinal contents, none existed in the bowel itself. The whole of the viscera of the animals were then examined together, to detect, if possible, a trace of activity, but with a negative result. These last estimations were made with the emanation electroscope.

Therefore while the contents of the bowels themselves are exceedingly active, the bowel wall and the other viscera show no evidence of any trace of radium.

Absorption, therefore, in the case of insoluble salts does not occur after administration by the mouth.

The next question that arises is the fate of these salts after subcutaneous injection. We must consider this under three headings :—

(1) The elimination of soluble salts of radium admixed with barium salts.

(2) The elimination of insoluble salts of radium.

(3) The distribution and elimination of pure radium salts.

1. *Experiment* to determine the direction of excretion of soluble salts of radium admixed with barium.

For this purpose two mice A and B were taken and injected subcutaneously with 0·5 mg. of radium barium bromide of 20,000 activity (uranium taken as unity). Both points of injection were painted with a solution of collodion in acetone, to prevent any risk of escape of fluid. Both mice were then placed in a cage specially constructed for the separation and collection of urine and faeces, which were removed at the end of every twenty-four hours. The excreta were examined in the emanation electroscope and the daily activity recorded. The charts (Plate XIV, Figs. 1 and 2) show the radio-activity of the urine and faeces for each succeeding twenty-four hours.

From this we see that 60–70 per cent. of the radium excreted appears in the faeces during the first twenty-four hours, and only 10 per cent. in the urine. At the end of the third day the amount has fallen to 2 per cent. in the faeces and practically nothing in the urine.

2. In the same way, to study the elimination of an insoluble salt injected subcutaneously, a mouse of 16 grammes weight was injected with 50 mg. of radium barium sulphate of 250 activity. A daily examination of the urine and faeces was made in all cases. The urine was negative and the faeces showed a very feeble radio-activity. The chart (Plate XIV, Fig. 3) indicates the daily

record of active material passed by the bowel. In all these experiments a control experiment was performed before the injection was given to test the normal urine and faeces for activity.

The chief features of this chart are the exceedingly small quantity of radio-active material eliminated each day, and the long time over which this excretion is prolonged. In this case the animal was still passing active faeces twenty-three days after injection.

In a second experiment a mouse was injected with the same quantity of radium barium sulphate and the accumulated faeces were examined at the end of the first fourteen days, at the end of the third week, two days later again, and then at the end of the fourth week.

The table shows the total radio-activity for each period.

Excretion.		Natural leak. Division per min.	Period of Collection.	Activity (total). Division per min.	Activity in scale division per day.
Urine nil	Faeces —	0·18	Dec. 21–Jan. 4	1·70	0·12
	—	0·22	Jan. 4–Jan. 11	0·84	0·12
	—	0·21	Jan. 11–Jan. 13	0·26	0·13
	—	0·22	Jan. 13–Jan. 20	0·85	0·12

We see that the amount excreted daily is constant, and identical with that excreted in the previous experiment. Again, if these figures really represent the presence of radium, we should expect to find that salt present at the seat of injection at a late date. In the last experiment, four days after the last estimation, or thirty-two days from the initial injection, the animal was killed, and the tissues at the site of injection were cut up and examined in the a-ray electroscope. There was marked activity present. An examination, in a similar way, of the other viscera showed a feeble activity in the liver alone.

In the above injection experiment radium has been used, diluted with barium. Now it has been shown by Gustave Meyer that elimination of this metal takes place almost entirely by the bowel, and only slightly in the urine, when the animal is fed by the mouth. It is therefore possible that the excretion of radium might be influenced by the presence of the barium. A further experiment was therefore performed with a small quantity of pure radium bromide, and the curves of excretion (Plate XIV, Figs. 4, 5, and 6) can be compared with that of radium barium bromide (Figs. 1 and 2). It will be seen that excretion takes place in almost the identical way and at the same rate in the two cases.

In this experiment two mice were used and an injection of 2 c.c. of distilled water containing 0·0036 mg. of pure radium bromide was given in each case. The radio-activity of this quantity of radium was estimated previous to use at about 800 div. per min. (0·2 c.c. of the original solution discharged an electro-scope at the rate of 40 div. per min.). If the activity for the various periods be added up, we find the total is 825. So that apparently all the radium originally given appears either in the urine or faeces, if we allow a small margin of 25 in a large number of readings to be due to an extra 0·1 c.c. having been injected or as due to repeated small errors of observation.

Of the total quantity 91 per cent. appears per rectum and only 9 per cent. in the urine.

From repeated experiments we can say that the excretion of radium, whether given by the mouth or by injection, appears to take place principally by the bowel, and to a slight degree by the urine. It then only remains to examine the distribution of the radium after injection and to discover whether the whole, or only a part, of the intestinal canal excretes radium, and whether any other organ, such as the liver, plays any part in the process.

William Salant and Gustave Meyer, working on the elimination of radium, found that in dogs and rabbits the kidneys, liver, and small intestine eliminate radium, while in rabbits elimination also takes place through the large intestine. In these experiments radium barium bromide of 1,000 activity was used and a dose of 10–30 mg. given on each occasion.

The means employed were the formation of a biliary fistula on the one hand and ligature of the different portions of the intestinal canal on the other. These ligatures were placed at the cardiac and pyloric end of the stomach, below the duct of Wirsung and above and below the caecum. An injection of radium was then given, the bile was collected at varying periods, and a few hours later the animal was killed. By this means in dogs they found the bile radio-active, as also the contents of the small intestine. The stomach, large intestine, and contents of both showed no activity.

The same features held true for rabbits, with the exception that there was some slight activity in the contents of the large intestine. In no case was any activity detected in the intestinal wall. These estimations were conducted by means of a quadrant electrometer, and are consequently of a purely qualitative order and give no indication of the quantity of radium present. In other words, the activity was measured by observing the ionization of the air in which the various organs were exposed, which does not give the total radium content, but depends on the area of the specimen exposed, and its density. Further, the mere evidence of activity in an organ or secretion does not indicate necessarily that that organ or secretion is actively eliminating radio-active material, unless it can be shown that the activity present is greater than the average activity elsewhere As will be seen from the experiments below, activity is present everywhere in the body and tissues generally, both with large and small injections of radium, after four hours or after twenty-eight hours from the time of injection.

With mice, it is impossible to conduct an experiment on the same lines as those of Meyer and Salant; another method, therefore, must be utilized to determine the proportion of radium present in the various parts of the body after an injection of a quantity of that element subcutaneously. The experiments that follow depend for their result on the measurement of the radium by the estimation of the emanation in equilibrium with it, a factor which is after a certain time a constant. This method is therefore quantitative and not qualitative alone, and if the weights of the different parts of the body be taken the percentage of radium present in each part can be deduced from the measurement of the emanation liberated.

There is, however, a difficulty in these experiments which after repeated trial has been found insurmountable, and that is the introduction of an exact quantity. It is obvious that the injection of the smallest fraction more or less than the amount calculated for will upset by many figures the total of the activities present in the body at the end of the experiment. No great trouble has been taken, therefore, to save and measure the excreta or to determine what is practically an impossibility, the value of the amount injected, but a series of careful observations on the distribution of the element throughout the body after administration has alone been undertaken.

Experiment I. Three mice were taken on June 29 and injected each with 2 c.c. of pure radium bromide solution. The total quantity of radium injected was about $\frac{1}{100}$ mg. The three mice immediately after injection were placed in a cage, so arranged that no excreta might be lost. Eighteen hours later they were killed and the rest of the experiment was carried out in the following stages: (1) The bodies were opened; the stomach, small intestine, and large intestine were each separately ligatured at their extremities and divided and placed in separate vessels. (2) Each in turn was then repeatedly washed until free from its contents, which were saved. (3) The other viscera were then removed and placed each in a small glass specimen-tube, previously weighed. (4) The skin was carefully removed from the rest of the trunk and each was similarly preserved in a separate receptacle. (5) The weights of the various organs and structures were then immediately taken in the wet state. (6) After one month each separate organ and portion of tissue was taken, minced finely in distilled water, placed in a small flask and gently heated; the products so obtained were collected in a wash-bottle series and conveyed to the emanation electroscope. By this means a measurement of the quantity of radium contained in each organ was obtained by the estimation of the emanation liberated. (7) The tissues were then all carefully dried in a water bath and afterwards in a sulphuric acid desiccator until the weight was constant. The percentage activity in dry and wet substance respectively was thus obtained.

The following table shows the radio-activity exhibited by the different parts of the body :—

Part of Body or Tissues examined.	Weight wet in grm.	Weight dry in grm.	Total Activity in divisions per min.	Activity in scale divisions per min., per 100 mg. of organ.	
				Wet.	Dry.
Skins	12·850	7·000	68·5	0·53	0·98
Trunks (muscles and bones) . . .	40·400	15·000	2100		
Livers and Gall-bladders	5·887	1·644	23	0·39	1·40
Kidneys . . .	1·452	0·400	8·5	0·59	2·12
Spleens . . .	0·722	0·201	4·7	0·65	2·33
Lungs	1·000	0·265	11·3	1·13	4·26
Hearts	0·602	—	0·04		
Genital Organs . .	4·687	3·123	18·1	0·39	0·58
Stomachs . . .	0·752	0·138	1·66	0·22	1·20
Small Intestines . .	4·057	0·899	25·0	0·62	2·80
Large Intestines . .	1·677	0·342	10·3	0·62	3·01
Contents of Small Intestines . . .	—	0·357	4·5		
Contents of Large Intestines . . .	—	0·200	11·1		
Contents of Stomachs .	—	—	0·3		
Faeces passed before death . . .	—	—	41		
Urine passed before death . . .	—	—	30		
Washings of cage trays, food, &c. . . .	—	—	218		

A second incomplete experiment shows features which are similar to above. In this experiment the same number of mice were taken and the same quantity of radium was administered subcutaneously. Injected on May 10—killed nineteen hours later.

Table showing various radio-activities.

Organs or Tissues examined.	Weight dry in grm.	Weight wet in grm.	Activity in scale divisions per min.	Activity in scale divisions per min., per 100 mg. in wet organ.
Livers and Gall Bladders	4·807	0·977	8	0·16
Lungs	1·027	0·168	6·3	0·61
Spleens . . .	0·962	0·158	2·0	0·21
Kidneys . . .	1·060	0·145	25	2·40
Small Intestines . .	0·780 ?	not weighed	1·09	0·14
Large Intestines . .	1·022	” ,,	6·0	0·58
Stomachs . . .	0·397	0·040	0·38	0·10
Contents of Stomachs .	not weighed	not weighed	0·34	—
Contents of Small Intestines . . .	,, ,,	,, ,,	109·00	—
Contents of Large Intestines . . .	,, ,,	,, ,,	150·00	—
Rest of Body . .	20·009	12·00	400·00	2·0

These figures will be commented on when the two next experiments have been described. For the present it suffices to draw attention to apparent enormous differences in the activity of the contents of the bowel in the two experiments. This is easily explained by the fact that two of the mice in the previous experiment developed diarrhoea after the injection and the bowels post mortem were virtually empty. In the second experiment the bowels were normal and contained a quantity of faecal material and consequently a quantity of radio-active material.

In order to confirm these results and also partially to see whether larger doses of radium are poisonous after injection, a third experiment was carried out. In this case $\frac{1}{44}$ mg. of pure radium in 0·5 c.c. distilled water was injected subcutaneously into a mouse on Aug. 5. No distress or ill effects of any kind were noticed during the following twenty-eight hours. The mouse was then killed and the organs and tissues were weighed separately, and then dried, weighed again, and kept sealed for a month in small glass specimen-tubes. At the end of that time they were examined by means of the emanation electroscope for radio-activity.

The table appended gives the figures :—

Female mouse, weight 18·300 grm., injected with 0·5 c.c. of radium bromide solution (4 mg. in 88 c.c.) Aug. 5 at 1 p.m. Killed 5 p.m., Aug. 6, twenty-eight hours after injection.

Organs or Tissues examined.	Weight wet in grm.	Weight dry in grm.	Activity in scale divisions per min.	Activity in scale divisions per min., per 100 mg. of organ.	
				Wet.	Dry.
Liver and Gall-bladder.	1·526	0·463	3·3	0·22	0·71
Lungs	0·579	0·135	24·0	4·1	17·7
Kidneys . . .	0·406	0·125	19·3	4·75	15·44
Spleen	0·197	0·052	4·4	2·23	8·50
Genitalia . . .	0·507	0·383	1·01	0·20	0·26
Stomach . . .	0·215	0·065	0·67	0·31	1·03
Small Intestine . .	1·162	0·240	2·07	0·17	0·86
Large Intestine . .	0·397	0·078	1·07	0·26	1·37
Skin ⎫ Body ⎬ . Muscles and Bones⎭	12·000	—	600	5·00	
Contents of Intestine and Excreta . .	Exceedingly active. No accurate estimate obtained.				

In the fourth experiment of the series $\frac{1}{22}$ mg. of pure radium bromide was injected subcutaneously on Aug. 8. As before, no ill effects or changes appeared as a result of the administration. The animal was killed $6\frac{3}{4}$ hours later. No changes post mortem could be demonstrated. The organs were treated as above.

Female mouse, weight 19·500 grm., injected subcutaneously with 1 c.c. pure radium bromide (4 mg. in 88 c.c. distilled water) at 11.15 a.m., Aug. 8. Killed 6 p.m., Aug. 8, $6\frac{3}{4}$ hours after injection. The estimation of radio-activity of organs and tissues is as follows :—

Organs or Tissues examined.	Weight wet in grm.	Weight dry in grm.	Total Activity in scale divisions per min.	Activity in scale divisions per min., per 100 mg. of organ.	
				Wet.	Dry.
Liver and Gall-bladder	1·526	0·518	4·2	0·27	0·81
Lungs	0·187	0·045	10·3	5·5	22·9
Kidneys . . .	0·302	0·077	50·0	16·5	65·03
Spleen . . .	0·287	0·070	1·17	0·41	1·67
Genitalia . . .	0·232	0·128	0·83	0·36	0·65
Stomach . . .	Weight lost	0·050	1·24	—	2 48
Small Intestine . .	1·715	0·375	8·0	0·47	2·13
Large Intestine . .	0·490	0·180	7·25	1·48	4·02
Skin ⎫ Muscles and Bones⎬ .	12·500	Not weighed	1875	15·0	
Blood	0·109	0·022	10·0	9·2	45·5

Now in all these four experiments a fact obtrudes itself constantly, and that is the high activity which is present in the lungs and kidneys, whether death has taken place shortly or some hours after injection, or whether the injection has been a powerful dose or a small dose. In three out of the four experiments the percentage is higher in the kidneys than in the lungs. The next feature is the total absence, apparently at any time after injection, of an accumulation of radium in the liver and gall-bladder. If this organ and the bile took an active part in elimination it would be natural to expect at some period a percentage higher than the average to be present. This is not the case. When we come to deal with the spleen we find the percentage activity is little if at all above the average in three cases, while in the fourth there is evidence

of quite a marked radio-activity. Had the activity in the spleen been constantly of a high character we might have assumed that along with the lungs such activity was due to the great vascularity of these organs. Now it will be shown later that the lungs are the chief path in the elimination of the emanation, and consequently, failing other explanation, we must assume that accumulation takes place in these organs for the purpose of freeing the radium from its active principle, the emanation.

The genitalia and stomach with the liver show no evidence in any of the experiments of any activity higher than the average. Further, the contents of the stomach, which are estimated, are practically nil, showing that no elimination takes place through the wall of the stomach. When we come to the small and large intestine, one or both of which most assuredly excrete the major quantity of the element, we are met at once with a difficulty, for the activity of the bowel wall—though it is generally slightly greater than the average, and is more marked in the large than in the small intestine—at no time shows any accumulation of radio-active material. Seeing, however, the great activity which is exhibited by the contents, we must assume that excretion takes place with such rapidity that the quantity present in the bowel wall is never much above that continually present in the blood-stream. Whether excretion takes place by the large and small bowel or by the small intestine alone can hardly be settled from these figures. But the greater activity of the large intestine throughout rather suggests that it also plays some part in elimination. Against this must be weighed the fact that the cleansing of the sacculated large intestine from its contents is more difficult than the same process in the small intestine.

The remaining structures to be dealt with are the skin, muscles, and bones. In the second experiment there exists no evidence that the skin plays any part in excretion. With the muscles and bones there appears to be a higher activity, but this is due to the fact that death has occurred in all cases before the absorption of the radium injected into the tissues has been completed.

For the normal distribution of radium in these tissues after administration, reference must be made to the experiment in which this element was given by the mouth. It will be seen that the quantity present is exceedingly low. We notice in this experiment also the same features as occur in the injection experiments, namely, a high activity in the kidneys, a much less activity than usual in the lungs but greater than that represented by the liver and tissues generally ; also a greater activity in the large intestine than in the small.

It appears, therefore, that however given, the absorption and elimination of radium salts takes place always in the same direction, and in the same ratios. That, further, the evident channels of excretion are the small and large intestine primarily, the kidneys next, and that for some reason or other an accumulation takes place in the lungs, which is only explicable by the theory that it is an effort on the part of the body to free the radium contained in the blood from the emanation in equilibrium with it.

Distribution and Excretion of Emanation.

So far we have dealt with radium and its salts. There still remains the emanation. The emanation is capable of administration in several ways: (1) by inhalation; (2) in solution: (*a*) by the mouth; (*b*) by injection.

That absorption from the lungs and a widespread and general radio-activity occur in the body after inhalation is shown by the following experiment: Two mice were placed in a partially exhausted vessel which was attached to a flask containing radium in solution. Air and emanation were allowed to pass slowly into the vessel containing the mice. After $3\frac{1}{2}$ hours' exposure, an examination of the viscera of one of these animals revealed a marked activity in all the organs examined, thus:—

Nat. leak of Electroscope.	Liver.	Lungs.	Kidneys and Spleen.
0·20 div. per min.	8·5 div. per min.	6·7 div. per min.	5·0 div. per min.

The next question is the administration in solution.

To prepare a solution of the emanation: place the liquid it is desired to activate in a vessel, exhaust the vessel, and attach to a flask containing a solution of radium in water. A gradual de-emanation of the radium in solution occurs by allowing a current of air to pass through the solution into the exhausted vessel. At the same time a great activity is induced in the liquid in the latter by absorption of the emanation carried over by the current of air.

To determine whether absorption of the gas takes place after administration of the radio-active liquid by the mouth, the following experiment was performed. A full-grown mouse was fed on seed and radio-active water, or sop made with radio-active water, from Sept. 3 to Oct. 7, during which period $90\frac{1}{2}$ c.c. were supplied. On the latter date the mouse was killed, two and a half hours after the last administration. A rapid examination of the viscera was made, by means of the *a*-ray electroscope, to determine whether any activity was present. A feeble but widely distributed radio-activity was found to be present.

With a view to testing the duration of this activity a second experiment was conducted with a mouse *B* fed in a similar manner from Sept. 20 to Nov. 15. During this period 240 c.c. of the radio-active solution were given. In this case the animal was not killed until twenty-four hours after the last food had been given. An examination on the same lines as before showed a total absence of any activity in the body. At the end of two or three hours, therefore, there is a very feeble activity, which is totally absent at the end of twenty-four hours. In other words, the activity induced in the different tissues of the body by feeding an animal on a solution of the emanation is only of a temporary nature. Now we know that the emanation only decays to half value in about four days, and that this rate is a constant; consequently, if it is absorbed and has disappeared in less than twenty-four hours, we must assume that it is either destroyed or is rapidly eliminated. As the first is impossible, excretion of the gas evidently takes place in some direction. Now in the feeding experiments it

is impossible to obtain the excreta or respiratory gases without previous contamination with the food material. Further, the quantity consumed at any one time is probably so small and is spread over so large an area after absorption, that any appearing in the excreta would be infinitesimal in quantity.

A number of observations were made on the urine and faeces and respiratory gases of animals fed on radio-active food, but no evidence of radio-activity was forthcoming.

With the injection of large doses subcutaneously it is different. And it is possible to demonstrate that when the gas is introduced in this manner both the direction and rate of elimination can be detected.

The first experiments were undertaken to determine whether any active gas appeared in the urine or faeces. A mouse, weight 25 grm., was placed in a cage for collection of urine and faeces. The specimens collected for the first twenty-four hours were examined and found to be free from any trace of activity. The mouse was then injected subcutaneously with 1 c.c. of radio-active distilled water at 10.45 a.m., Dec. 2. The urine was collected over short periods and the activity estimated in the usual way by the emanation electroscope. The following table gives the various figures :—

Quantity of radio-active fluid injected.	Time of Injection.	Duration of Collection.	Natural leak of Electroscope. Div. per min.	Activity of Urine. Div. per min. Natural leak deducted.
(1) 1·0 c.c. (40 div. per min.)	10.45 a.m., Dec. 2	10.45 a.m.–12.45 p.m.	0·133	1·58
(2) 1·0 c.c. (40 div. per min.)	10.45 a.m., Dec. 2	12.45–4.45 p.m.	0·22	0·07
1·0 c.c. (40 div. per min.)	10.45 a.m., Dec. 2	6.30 p.m., Dec. 2, to 10.30 a.m., Dec. 3	0·18	0·05

It would appear, then, that when the emanation is introduced subcutaneously in water, a very small quantity appears in the urine of the first two hours, while after that period the activity of that excretion is scarcely perceptible. Further, as a previous estimation of the radio-active liquid used showed that 1 c.c. possessed an activity capable of discharging an electroscope at 40 div. per min., it is clear that the greater portion of the emanation must escape other than through the kidneys. The faeces gave no evidence of activity. The two following experiments show similar results, but not so marked, owing to the fact probably that a larger interval occurred before the urine was collected in the first instance.

Experiment I.   A mouse was injected on Oct. 18, at 10.45 a.m., with
2·5 c.c. of radio-active distilled water (activity of 1 c.c. = 433 div. per min.).

Quantity injected.	Time of Injection.	Period of Collection.	Natural leak. Div. per min.	Activity of Urine. Natural leak deducted.
A. 2·5 c.c.	10.45 a.m., Oct. 18	10.45 a.m. to 5.45 p.m.	0·13	0·10
B. (1) 2·5 c.c.	11.5 a.m., Oct. 26	11.5 a.m. to 4.20 p.m.	0·11	0·08
(2) 2·5 c.c.	11.5 a.m., Oct. 26	6.30 p.m., Oct. 26, to 10.30 a.m., Oct. 27	0·12	0·00

Experiment II.   The same animal was injected again on Oct. 26, and the
result is shown in table B (1 and 2).

As in these experiments the direction of excretion of the radio-active gas was
probably influenced by the presence of an excess of water in the tissues, tending
to diuresis, a second series of experiments was made with an active solution in oil,
a vehicle which is hardly or not at all absorbed, and is therefore incapable of
influencing the excretion of the gas contained in it.

Experiment I.   A mouse was injected on Dec. 13, at 12.30 midday, with
1 c.c. of oil having an activity of 1,000 (1 c.c. = 1,000 div. per min.). The table C
below gives the times during which the excreta were collected and the activities
of each respectively.

Quantity and Activity of Oil.	Time of Injection.	Period of Collection.	Natural leak. Div. per min.	Activity of Faeces. Natural leak deducted.	of Urine.
C. 1 c.c. (1,000 div. per min.)	12·30 p.m., Dec. 13	6.30 p.m., Dec. 13—10.30 a.m., Dec. 14	0·18	0·00	0·00
	12.30 p.m., Dec. 13	Dec. 14—16	0·16	0·00	not esti-mated

Experiment II.   On Feb. 18, at 5.30 p.m., a second mouse was injected
with 1 c.c. of oil (activity = 1,600 div. per min.).   Table D shows the activity of
the excreta.   The injection was repeated on Feb. 21.   Vide table E.

Quantity and Activity of Oil.	Time of Injection.	Period of Collection.	Natural leak. Div. per min.	Activity of Faeces. Natural leak deducted.	of Urine.
D. 1 c.c. (1,600 div. per min.)	5.30 p.m., Feb. 18	5.45 p.m., Feb. 18—3.30 p.m., Feb. 19	0·15	0·00	0·27 possibly contami-nated
E. 1 c.c.	11.30 a.m., Feb. 21	11.30 a.m., Feb. 21—10.30 a.m., Feb. 22	0·066	not esti-mated	0·00

From these we see that while the specimen of urine collected for twenty-two
hours after injection on the 18th gave evidence of high activity, that on the
21st gave none.   Similarly the excreta in C show no radio-activity.   The mouse
injected on the 18th and 21st of Feb. was killed on Feb. 24, and the tissues at
the point of injection were carefully examined.   Although oil was present, there
was no radio-active material.   That is, by the third day all the active gas had

escaped. It is possible in the experiments that, as no examination was made of the urine until a good many hours after injection, the little radio-active gas passed by the kidneys might have previously escaped. Consequently a third mouse was injected with 1·2 c.c. of oil on Feb. 25, at 12.35 p.m. The urine was collected for the following five hours. Vide F.

On Feb. 28 a fourth mouse was injected with 1·6 c.c. and the urine passed in the following three hours estimated. Vide G.

It will be seen in both cases that a very feeble activity exists, which, as we shall be able to show later, is possibly due to some absorption of the emanation excreted by the lungs.

Quantity and Activity in div. per min. per c.c.		Time of Injection.	Period of Collection.	Natural leak of Electro-scope.	Activity of Urine. Natural leak deducted.	of Faeces.
F.	1·2 c.c. (1,600)	12.35 p.m., Feb. 25	12.35–5.35 p.m., Feb. 25	0·055	0·105	0·00
G.	1·6 c.c. (1,600)	12.30 p.m., Feb. 28	12.35–3.35 p.m., Feb. 28	0·086	0·044	0·00
	1·6 c.c. (1,600)	12.30 p.m., Feb. 28	6.30 p.m., Feb. 28—10.30 a.m., March 1	0·067	0·031	0·00
	1·6 c.c. (1,600)	12.30 p.m., Feb. 28	6.30 p.m., March 1—10.30 a.m., March 2	0·071	0·00	0·00

In one only of these experiments, then, is there definite evidence of activity in the urine, while the faeces were negative throughout. Two other channels of excretion remain, namely, the lungs and skin. The latter, we have seen after the administration of radium bromide by mouth, exercises no excretory function (p. 250). We are left, then, with much the most probable channel, namely, the lungs.

Before estimating the activity of the exhalations of an animal injected sub-cutaneously with radio-active liquid, it is perhaps advisable to see how long this activity persists at the site of injection. We have seen from the above experiments that from four to seven days after injection there is no evidence of activity in the oil left at the point of injection. Further, when the emanation was injected in water, such activity as appeared in the urine was only evident during the first two hours of excretion.

With these data, on June 6 at 2 p.m. a mouse was injected with 1 c.c. of oil (having an activity of 6,000 div. per min.). The animal was killed at 5 p.m. the same day. The tissues at the seat of injection were removed *en masse*, heated in a flask, and the products so obtained admitted into an exhausted electroscope.

It was then found that the oil left after three hours possessed an activity of only 88 div. per min., while the entire viscera discharged the electroscope at 4·2 div. per min. The rest of the body was not examined. It is evident, therefore, when we compare the activity of the oil previous to injection and

three hours after injection, that the elimination of the emanation is exceedingly rapid.

The following experiment shows that this elimination takes place almost entirely, if not completely, by the lungs :—

Experiment. A large glass vessel of 1,200 c.c. activity, fitted with an air-tight stopper and two glass tubes bent at right angles, was taken, and in it was placed a mouse, previously injected subcutaneously with 1 c.c. of oil (activity = 6,650 div. per min.). No attempt was made in this experiment to collect all the emanation expired from the lungs. The jar was in communication on the one hand with the air of the room, and by the other tube with an emanation electroscope. The mouse was injected at 12.15 and placed in the jar at 12.23 p.m. At varying periods after this time samples of contained air and emanation were withdrawn into the electroscope, and the activity of the sample so removed was estimated. The following table indicates how the activity of the air contained in the vessel falls as the quantity of emanation expired begins to decrease. The first column shows the times at which a sample was removed for estimation. Thus the first estimation was made fifteen minutes after the mouse was placed in the vessel, the second fifteen minutes after that, the third forty minutes later, and so on. The second column gives the estimated activity of the sample, and the third column gives the average activity of the amount discharged per minute of each period of time.

Sample.	Time at which sample was withdrawn.	Activity of sample. Div. per min.	Activity of amount discharged per min.
(1)	12.38	545	36
(2)	12.53	436	29
(3)	1.33	920	23
(4)	2.5	568	18
(5)	2.42	683	18
(6)	3.12	428	14
(7)	3.44	428	14
(8)	4.42	262	4

This experiment gives no idea of the total quantity of emanation excreted by the lungs from hour to hour. Accordingly a second experiment was prepared to measure the actual rate of elimination after the injection of a known quantity. For this purpose a large jar of 1,205 c.c. capacity was taken and fitted with an air-tight stopper and entrance and exit tubes, each tube having a tap. Two wash-bottles containing water and connected in series were also fitted up. A mouse was then injected subcutaneously with 1 c.c. of oil, activity = 3,000 div. per min. The injection was given at 3 p.m. and the mouse was immediately placed in the jar, which was then tightly closed and clamped. After a period of twenty minutes the exit tube of the jar was attached to the entrance tube of an exhausted emanation electroscope. The taps between jar and electroscope were opened and a portion of the emanation and air contained in the jar was thus drawn into the electroscope. The partially exhausted jar was now attached to the wash-bottles, and the taps between these and the jar were in turn opened and air was withdrawn from the wash-bottles to replace that which had passed into the electroscope. By measuring the quantity of water displaced from one wash-bottle into another the amount of air and emanation withdrawn by the electroscope could be estimated.

The jar containing the mouse was now rapidly cleaned out and dried, the mouse replaced, and after a further period of time had elapsed a second quantity of emanation was withdrawn, and so on until three hours had passed since the injection. By this means, knowing the quantity of emanation and air removed on each occasion and the total capacity of the jar, it was possible to determine the quantity of emanation excreted during each period, per hour or half-hour as the case might be.

The various readings for the three hours are shown below :—

Time of injection, 3 p.m.   Capacity of jar, 1,205 c.c.

Period of Collection.	Quantity withdrawn in c.c.	Activity in div. per min.	Total Amount exhaled.	Average Amount exhaled per min. during Period of Collection.
3.03–3.23	390	200	618	30·9
3.33–4.28	390	345	1065	19·9
4.33–5.03	370	89	290	9·7
5.14–5.54	340	78	278	(7·5)
6.03–6.18	207	9	52	3·5

Hence we see that the total activity of the emanation collected amounts to 2,303 div. per min. when the quantity injected had a value of 3,000 div. per min. But we have not yet calculated for the short periods during which the animal was removed from the jar for cleaning purposes and during which time the emanation would consequently be lost. We can, however, arrive at a rough determination of the value of this amount in the following way : The total activity of the quantity excreted in the first twenty minutes is 618, that is to say, in every minute a quantity is discharged having an activity equal to $\frac{618}{20}$ or about 30 div. per min. Similarly in the next fifty-five minutes the quantity eliminated per minute has an activity equal to $\frac{1065}{55}$ or 20 div. per min. Between these two readings there is an interval of ten minutes. If we take the mean of the two readings above as the value of emanation emitted per minute during the interval, we shall arrive at a total quantity of activity lost equal to $25 \times 10 = 250$ div. per min. In the same way, by taking the mean of the reading before and after the interval, we can estimate the values of the amounts lost on each occasion. These happen to be 250, 70, 99, and 114 respectively, or a total of 553 div. per min. If we add this to our previous total of 2,303, we shall have accounted for 2,856 of the 3,000 injected.

The two totals therefore closely agree, and we see then that the elimination of the emanation takes place entirely by the lungs.

Conclusions.

1. That after the administration by mouth or by injection of radium a widespread degree of radio-activity is evident throughout the body.

2. That elimination of radium takes place principally and rapidly by the bowel, in a minor and slower degree by the kidneys, while in mice at all events there is no evidence that the liver or skin plays any part in excretion.

As regards the elimination of the element by the bowels, it is certainly excreted by the small intestine, and there are indications that the large bowel also assists in that function.

3. That the high activity in the lungs is possibly due to the extreme vascularity of these organs, but its constant presence at all times after inoculation and the fact that the emanation is entirely eliminated by the lungs suggests that an accumulation of radium takes place with a view to the more ready excretion of the emanation.

4. That the emanation can be obtained in solution in various media, and can be introduced into the body in small doses by inhalation, feeding, or by injection.

5. That after such administration, and however introduced, a general radio-activity of very brief duration is caused throughout the body.

6. That elimination of the emanation takes place principally and almost entirely by the lungs, and to a very slight extent by the kidneys.

7. That the duration of the activity induced in the body, or in other words the time taken in excretion, differs with regard to the nature of the preparation used. Soluble salts of radium are rapidly eliminated, however administered. The insoluble salts per os are excreted directly by the bowel and there is no evidence of any temporary absorption and circulation. When given by injection, however, an exceedingly slow elimination takes place by the bowel. The time taken, however, is so great that for all intents and purposes the salt may be considered to be permanently present at the site of injection.

8. The elimination of the emanation occurs with great rapidity and was complete, after administration in powerful doses, in so short a time as four hours.

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Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6
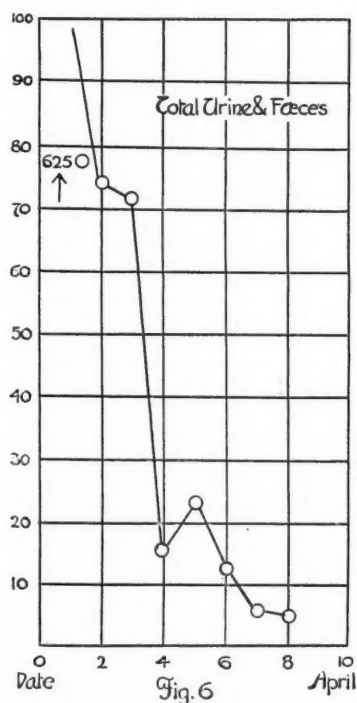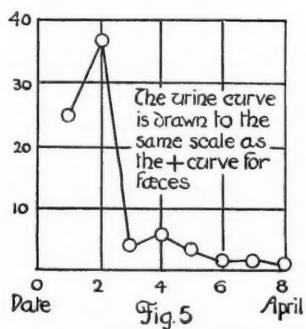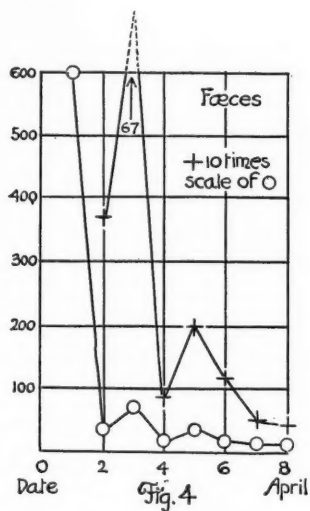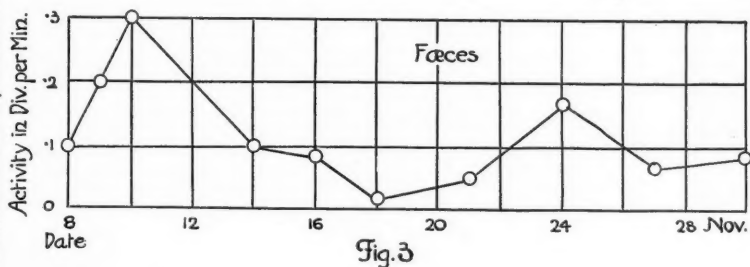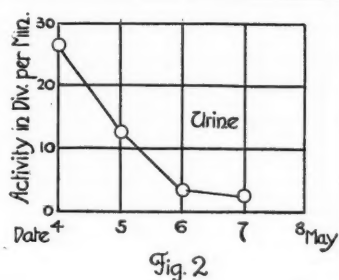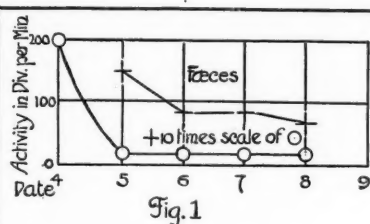
TWO CASES OF PAROXYSMAL BRADYCARDIA (TOTAL)

By E. E. LASLETT

THE two cases here described are alike in that in both the slow heart-beat is paroxysmal and that in both the infrequent pulse-rate is due to a true or total bradycardia in which both auricles and ventricles participate. The condition in both is therefore distinct from heart-block. The two cases, however, probably belong to distinct types. In the first the paroxysms of bradycardia are very short and so frequent that the pulse-rate is as often as not much below 60 per minute. In the second the single paroxysm observed was very long, and it is probable that such paroxysms occurred only in association with the peculiar cerebral attacks described.

Case I. The patient was a married woman, aged 53, who had had eight children. She was tall and spare; the face showed a fair amount of colour, but she had a somewhat careworn and weary expression. She had had very good health up to a year previous, never before that time requiring medical attention except for her confinements. In the summer of 1910 she had an attack of 'colic' which laid her up for some weeks, and she had never been quite well since. The immediate cause of her consulting me was that she had been suffering for a week from frequent and painful micturition. At this time (March, 1911) it was noticed that the pulse was very irregular and intermittent and on the whole slow. Usually no heart-sounds could be heard during the intermissions, and it was therefore probable that they were not due to extra-systoles, but either to heart-block or to a slowing of the whole heart. Ten days later she had a smart haemorrhage from the bladder and passed a large calculus, and in a few days the bladder symptoms completely subsided. The pulse then gradually increased in average frequency and in a week it was almost normal, and it was thought that the bradycardia had possibly been associated with the condition of the bladder. A few days later, however, the pulse irregularity reappeared and the heart since that time continued in about the same condition as when she was first seen.

Present condition. The patient told me that she had never fainted in her life. She had, however, frequent attacks of giddiness which were sometimes severe. The attacks occurred on coming downstairs, or on rising from a chair, but chiefly when she first got out of bed in the morning. At these times she was often compelled to seize hold of the bed-post for support and stand for a few moments before she was able to dress. A noteworthy symptom was marked lassitude and weariness which practically prevented her doing her housework. Judging from frequent observation this physical disability seemed to correspond fairly closely with the degree of bradycardia, and on days when the pulse was more regular and frequent she voluntarily stated that she felt much stronger and brighter. Pain was not a common feature, but on one or two occasions when the pulse intermissions had been long and frequent she complained of

a more or less constant gnawing pain under the left breast. Although she was not anaemic she readily became short of breath after any slight extra exertion.

Heart and pulse. The heart-sounds were normal, without murmur, and there was no increase of cardiac dullness. The apex beat was weak, hidden by the breast, and it was not possible to obtain a cardiographic curve. During the intermissions no sounds were heard except when extra-systoles occurred as described below. The pulse was of moderate tension and rather small volume. It was rarely regular for any lengthened period, when the patient was sitting or standing. The frequency on the whole was very variable according to the number and length of the intermissions, but was rarely above 60 per minute. When the patient lay down the irregularity tended gradually to disappear within a few minutes as a rule, and then the rate was usually about 60–64 per minute. On frequent occasions it was noted that the pulse became markedly slow and irregular immediately the patient sat up. This is important in relation to the time when the vertigo was most likely to occur. It was remarkable as a rule how little the pulse frequency rose in response to the ordinary exciting stimuli such as emotion or exertion. On one or two occasions I have found the pulse quick, up to 100, when the patient has been visited unexpectedly in the midst of her housework. Moderate exertion had little quickening effect. After the effort of mounting the steep stairs in her house, which is a considerable trial to her, the pulse remained infrequent and showed the long pauses as usual. Sipping, tried on one occasion, caused one quick beat to appear, but the subsequent pulse-rate was hardly altered. As will be described later, a certain number of the intermissions felt by the finger were really interrupted by the occurrence of single and multiple ventricular extra-systoles, which are feebly represented in the pulse curve, and were imperceptible to the finger.

Although a true intermission might last for two seconds and one with an extra-systole for nearly three the patient had absolutely no abnormal sensation referred to the region of the heart and recognized by her as associated with their occurrence. The lassitude and general weariness were coincident with the presence of long intermissions and low average pulse frequency, and it is reasonable to suppose that the attacks of vertigo were due to the occurrence of unusually long intermissions, whether these affected the whole heart or were interrupted by single or multiple ventricular extra-systoles. These extra-systoles barely affected the circulation—they were poorly represented in the carotid as well as the radial artery, and it is probable that the vertigo resulted from the accompanying cerebral anaemia. Up to the present the interference in the cerebral circulation has never been sufficiently prolonged to cause insensibility.

Pulse curves. Fig. 1 represents one typical form of the arrhythmia, in which a long intermission occurs followed by others of gradually diminishing length. There is no sign of auricular activity between the beats; the intermissions must therefore be due to arrest of auricles as well as ventricles. The *a–c* interval is constant for all the periods at one-fifth second. The sinus arrhythmia here shown is most characteristic. It is of high grade and peculiar form. The rhythmic periods are independent of respiration, as simultaneous respiratory curves show; indeed it is obvious that they are of much longer duration than the respiratory periods, as respiration was at the normal rate of 15–18 per second. Further, it is different from the short periodic variations which are characteristic of the youthful form of irregularity (Mackenzie), and which are frequently dependent in some way on the respiratory movements. At times when the pulse is not so slow the periods are of longer duration and may include 12 to 15 beats.
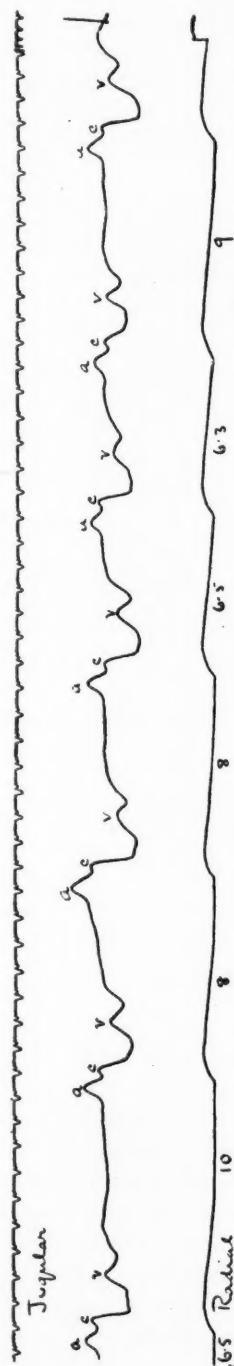
FIG. 1. To show a series of infrequent beats with the characteristic gradual increase in rate. The a-c interval is $\frac{1}{5}$ second for all the periods. The curve shows also that there may be a comparatively sudden diminution in frequency; the period immediately before the first long pause was $\frac{6.5}{5}$ sec. S., May 16, 1911.

The time marker in all the curves indicates fifths of a second. The figures below the radial curve in this and other tracings give the duration of the pulse periods in fifths of a second.
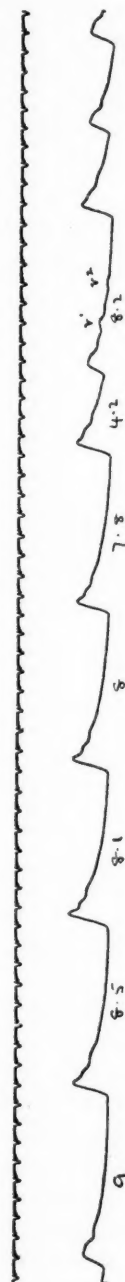
FIG. 2. To show a short series of infrequent beats with gradually diminishing frequency. Towards the end of the curve two extra-systoles occur in succession. S., June 5, 1911.
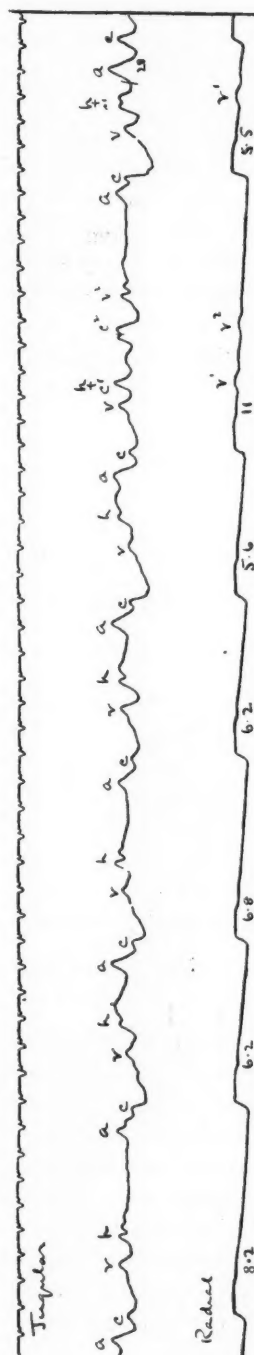
FIG. 3. Shows a series of infrequent beats, next two extra-systoles in succession. The small peak immediately preceding c^2 is left unfigured. It occurs midway between the preceding and following a waves and may therefore represent the auricular systole. It is possibly, however, a wave connected with c', as in such a position one would expect an exaggerated wave if it were due to the auricle as in the interpolation which follows. After the interpolated extra-systole the a-c interval is apparently increased. S., April 6, 1911.

The radial curve in Fig. 2 illustrates another less frequent form in which the bradycardia may appear. The series of slow beats begins and ends abruptly after a variable duration. The longest of which a record was obtained included eight beats at a rate of 34 per minute. In the figure the pulse-rate is 36. The first and last periods of the series are approximately double the duration of those immediately preceding and following it respectively.

Extra-systoles. In all the records obtained the extra-systoles are of ventricular origin. They occurred singly or in groups of two or three in succession. Up to the present no record has been obtained of more than three successive extra-systoles between two normal heart-beats.

FIG. 4. Radial curve to show an interpolated extra-systole during a series of slow beats. Pulse 40. S., May 3, 1911.

FIG. 5. Shows an interpolation where the succeeding *a–v* interval is normal. S., April 6, 1911.

Where a single extra-systole is followed by a so-called compensatory pause, this is of variable duration. Sometimes it is longer than the sum of the two preceding pulse periods, sometimes the same or shorter. It is naturally dependent on the degree of sinus activity. An example of a single extra-systole is probably shown at the beginning of Fig. 7, although there is a slight indication of a second premature wave in the radial curve. The large wave in the venous pulse which follows the extra beat is double peaked. This is so also in other records obtained, and the interpretation is not clear. The first peak is apparently due to the auricle, for it occurs midway between the neighbouring auricular waves. The nature of the second peak is doubtful, and I do not venture to give any explanation.

FIG. 6. At the beginning of the curve there are two extra-systoles. Note the well-marked *a* wave occuring just later than *c*³. Then follows an interpolation, with an apparently increased *a–v* interval succeeding it. Next follow three successive extra-systoles during a long auricular pause. S., April 6, 1911.
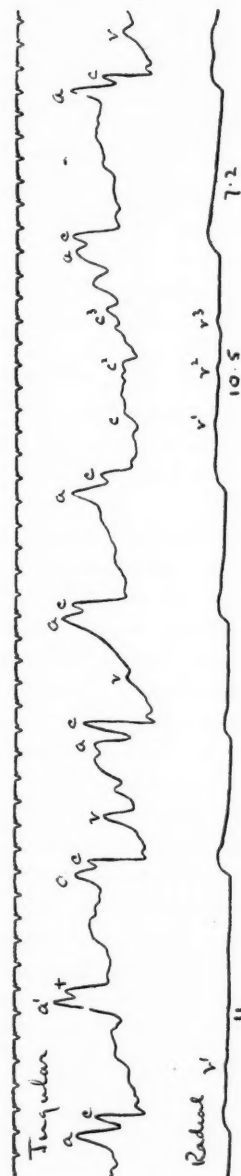
FIG. 7. A single extra-systole shown at the beginning of the curve. The wave marked *a'* probably represents the next following auricular contraction. The nature of the peak marked with a cross is obscure. At the end of the curve three successive extra-systoles occur during a long auricular pause. S., May 8, 1911.
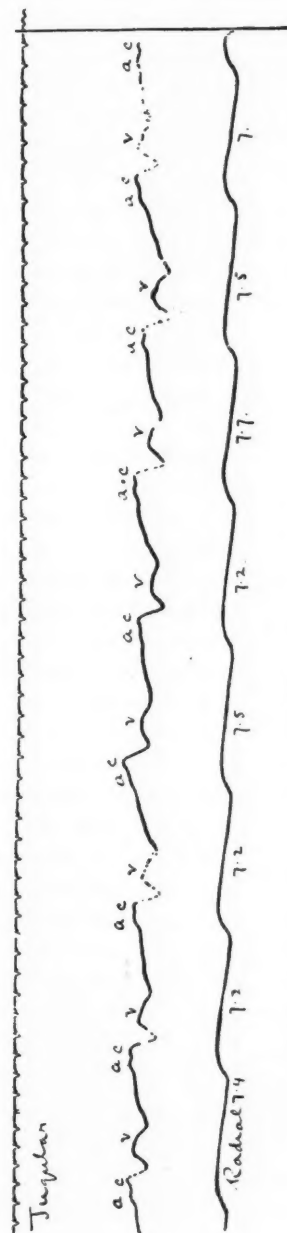
FIG. 8. To show that the auricles and ventricles contract at the same rate. The *a–c* interval is normal. Sh. (Case II), June 1, 1910.

Interpolated extra-systoles. Lewis (1) has shown by electro-cardiograms that the appearance of an interpolated ventricular extra-systole may be simulated by the occurrence of two successive extra beats, and the curves in this case in some examples illustrate the possibility of confusing the two conditions. The second extra beat may occur at such a point as to give the impression that it was due to the normally occurring auricular systole with a lengthened $a-v$ interval. The radial curve, if good, is usually sufficient indication as to whether the beat following the first extra-systole is of auricular origin or not, but instances have occurred in this case where the differentiation was not easy. Many times two interpolation periods occurred in succession, and were sometimes followed by an extra-systole with a following pause. This, of course, is conclusive evidence that they were true interpolations. Such a true interpolation is shown at the end of Fig. 3 and in Fig. 6. The $a-v$ interval of the following normal beat is apparently increased. In Fig. 5 there is an interpolation period of $\frac{6\cdot5}{5}$ seconds. Here the $a-v$ interval is normal, possibly because a occurs later after c^1 than in Fig. 3. It must, however, be borne in mind that slight differences based on a venous curve alone must be viewed with caution. There is always the possibility, where the intervals are short, of the superposition of v and h (Gibson) waves on a.

It is somewhat remarkable that interpolations were much more common in this patient when the pulse was at its highest frequency than when it approached 40 per minute. Only one or two examples have been met with when the pulse periods were longer than $\frac{7}{5}$ sec. (Fig. 4). When the pulse was slow multiple extra-systoles and single extra beats followed by a pause were much more frequently met with than interpolations.

Multiple successive extra-systoles. Examples of these are shown in Figs. 3, 6, and 7. At the beginning of Fig. 6 there is an intermission showing two extra-systoles. Here the auricle contracts at its normal time just after the second extra-carotid wave. At the end of the curve three extra beats occur. There is an element of doubt as to the interpretation in this instance. The radial curve is poor and it is possible that the irregularity consists of two interpolation periods. The jugular curve is, however, strong evidence against this, as all the extra-carotid waves are feebly represented and there is no evidence of an auricular wave at all. Other examples, such as that at the end of Fig. 7, are, moreover, quite definite in the radial curve. Here there is certainly no auricular contraction during the intermission of just over two seconds. At the end of Fig. 3 two extra-systoles occur in succession. Here again the auricular contraction fails, although it is possible that the peak immediately before c^2 is an auricular wave. In such a position, however, one would expect a large a wave, and it is therefore more probably a ventricular wave connected with the preceding extra-systole.

Sinus arrhythmia is almost certainly due to varying vagal control over the heart. It is a form of irregularity which is very common in the young, in whom

it may be of high grade. In adult and middle life it is believed to be comparatively rare. In adult patients Mackenzie has found it during convalescence from fevers and in his X disease. Marked sinus arrhythmia is very rare at and beyond middle life. Stokes (2) has recently described a striking example in a woman of thirty-six, in whom it was associated with anginal attacks of the vasomotor type. For the most part Stokes's case conformed to the youthful type, the rhythmic periods being short, while the normal pulse periods were well above 60 per minute. The long pauses, which usually occurred singly, were frequently just double the duration of the preceding normal pulse period, a relation which suggested the possibility of sino-auricular block. In other examples this interpretation would not serve, and as the pulse reacted in the usual way to atropin, the arrhythmia as a whole was regarded as of vagal origin. In the case here described, in some examples the first and last of a series of long pauses were sometimes exactly, sometimes approximately (to within one-tenth second or thereabouts) double the duration of the pulse periods immediately preceding and following the series. In others, however, no such relation existed. The unusual characters of the arrhythmia were : (1) The degree of bradycardia as a whole; the pulse periods were rarely below one second in duration. (2) The slow irregularly rhythmic variations in the sinus rate, independently of the respiration.

In order to ascertain the origin of the bradycardia $\frac{1}{60}$ grain of atropin was given hypodermically at a time when the pulse was continuously slow and irregular (40–42). Within half an hour the pulse-rate increased to 78 per minute, and the irregularity disappeared, with the exception of an occasional ventricular extra-systole. The vagal origin of the arrhythmia may therefore be considered as certain in this case.

It has been generally held that the vagus nerve has little direct control over the ventricular rate. Lewis (3) has, however, shown recently that a ventricular tachycardia retrograde to the auricle is in many instances inhibited by vagal stimulation. The vagus has therefore a direct action on the ventricle in a percentage of mammalian hearts. The occurrence of ventricular extra-systoles, single and successive, in association with and during the long auricular pauses has not been previously described, so far as I am aware. Such an association may be regarded as evidence that the excitability of the ventricle in this patient, so far as it concerns the formation of ectopic impulses, is little affected by the vagus.

Case II. The patient, a man aged 45, was slight and rather below the average height. He had a ruddy complexion, a good constitution, and enjoyed fair health. He had been under my care on and off for several years with slight ailments. Up to a year previous the pulse was always rather slow, 60–64 per minute; on one occasion he had a sharp attack of influenza with fever, during which the pulse remained at its usual rate. The heart was apparently normal and there was nothing of note as regards the other organs of the body. He had for several years had brief 'seizures' at varying intervals, perhaps eight or twelve in a year. The attacks were very brief and might occur at any time of the day, but usually when he was going about his business as an

insurance agent. He was generally made aware, by some indefinite sensation, of an impending attack. His statement was that he momentarily 'loses himself', then quickly recovers his senses and feels a little dazed and ill for a time.

The description agrees very well with the characters of a minor epileptic seizure. Bearing in mind, however, his rather slow pulse it seemed possible that they might be attended or caused by a further paroxysmal depression of the heart frequency. I have never witnessed an attack, but last year (June) I was sent for hurriedly because he had had an unusually severe one, and had been taken home in a cab. It appeared that while in a client's house he suddenly felt ill, just managed to get outside and sit down on the step, and then lost consciousness. On this occasion he felt more than usually dazed and ill, and when I saw him, about an hour later, he was cold and shivering and appeared very miserable and weak. The pulse was then only 32 per minute, regular and of small volume. Unfortunately I was not then able to take a pulse curve, but returned an hour later and took a long curve, of which Fig. 8 represents a portion. The pulse had risen to 40. The jugular curve is poor, as owing to the shivering it was impossible to get the neck muscles sufficiently relaxed. It is, however, clear that the venous pulse is of the auricular type and that there was not heart-block, the auricles beating at the same rate as the ventricles. The radial pulse is almost regular, with only very slight variations in the duration of the periods. Next day the pulse had increased to 50, and the patient felt quite himself. The following day the pulse had regained its usual rate of 60 per minute.

This brief record, based as it is on a single observation, may seem hardly justified. It seems, however, interesting as further evidence of the occurrence of repeated cerebral attacks associated with and not improbably caused by paroxysmal total bradycardia, as distinct from heart-block. It is, moreover, important as regards the prognosis in some of these patients. The occurrence of such attacks is more likely to cease and to be of less serious import than true minor epilepsy. This view was justified in the second patient; since the severe attack described he has had no further seizure, and when I last saw him in April of 1911 his pulse was 72, and he said he felt much happier about himself. This type of bradycardia associated with more or less slight syncopal attacks may ultimately prove to be more common than has hitherto been supposed. Mackenzie (4) refers to a man of fifty, whose usual pulse-rate was 60 per minute. He had syncopal attacks, and during the time that these occurred the pulse-rate was 40. He had been quite free from the attacks for some years. In the present case it is possible that the slow heart-beat was in some way dependent upon flatulent dyspepsia, from which the patient suffered, though not to a marked extent.

As the atropin test was not applied the true nature of the bradycardia was undetermined, but its apparently sudden onset would suggest vagal influence. On the other hand, the absence of sinus arrhythmia and the very gradual resumption of the normal rate distinguish this case from the few instances of true bradycardia which have been proved to be due to increased inhibition.

Summary.

The first case described exhibited sinus arrhythmia of a grade which is unusual at any age and very rare beyond middle life.

During the long auricular pauses multiple ventricular extra-systoles occurred.

The patient suffered from attacks of giddiness which it is suggested were due to cerebral anaemia induced by the long intermissions of the pulse.   The longest intermission so far observed was $2\frac{1}{2}$ seconds in duration.

The arrhythmia temporarily disappeared after the administration of atropin, and was therefore in all probability vagal in origin.

In the second case a true bradycardia of almost regular rhythm was found shortly after one of the cerebral attacks from which the patient suffered.   It is suggested, though not proved, that the infrequent rate of the heart was due to increased inhibition.

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CARDIO-RESPIRATORY MURMURS

By CAREY COOMBS

THE term 'cardio-respiratory murmur' covers those sounds which imitate cardiac bruits but bear internal evidence of a respiratory origin. The remarks in this paper are based upon notes of 180 patients, in examining whom I heard sounds of this type.

Discrimination of cardio-respiratory from cardiac bruits. As a rule this is not difficult, though the murmurs included in Group I below may imitate those of congenital pulmonary stenosis very nearly. The following points should be noted :—

(*a*) Respiratory variation. A murmur louder in inspiration is sure to be exocardial.

(*b*) Postural variation. A murmur heard only when the patient is in one particular position is probably exocardial.

(*c*) Cardiac time. Cardio-pulmonary murmurs are generally mid-systolic, separated by a definite interval from the preceding first sound.

(*d*) Character of the murmur. It is brief, begins and ends abruptly, and seems nearer to the observer's ear than the cardiac sounds.

(*e*) Distribution of the murmur. It is often narrowly localized; but even if it is not, it does not follow any of the common murmur-paths.

Classification of the cardio-respiratory murmurs. Two definite groups emerge from my 180 cases; the remaining 18 patients are mainly those in whom sounds of a definitely frictional character were heard, differing in one or more important particulars from the sounds typical of the two groups in question.

Group I (29 cases). The murmur is heard chiefly or solely at the base of the heart, especially at the pulmonary cartilage; it varies with respiration and posture, but not according to any definite rule. It is usually but not always systolic, and may be either whiffing or rubbing in character. As a rule it is brief, and remarkably limited in area. It is very often associated with pulmonary collapse in children (72 per cent.), especially if it be the anterior part of the left upper lobe that is collapsed.

Group II (133 cases). These are the patients in whom was heard the sound which usually goes by the name of the cardio-respiratory murmur. It has certain characteristics.

(*a*) It is always systolic, mid- or late-systolic as a rule.

(*b*) It is usually loudest during ordinary inspiration (74 per cent.) and

abolished by deep inspiration and by expiration. It may, however, be heard in expiration as well as in inspiration (9 per cent.), or even in expiration only (17 per cent.).

(c) As a rule, the murmur is lessened or abolished when the patient lies down on his back (74 per cent.).

(d) Generally it is heard best just outside the apex-beat; it is audible also along the left border of the heart (61 per cent.), often at the left base below the angle of the scapula (20 per cent.), sometimes along the right praecordial margin (11 per cent.).

(e) It is short, beginning and ending abruptly without any diminuendo or crescendo phase. The commonest type is a short puff, something like that of a steam engine; this may fall once, twice, or even thrice in one inspiration. There is every grade of variation from this brief, abrupt puffing sound to one which is definitely scratching and clearly caused by gross friction.

These murmurs are of course not uncommonly heard in quite normal persons; nevertheless, they are especially likely to occur in patients with pulmonary tuberculosis, and in subjects of nervous excitement. In both of these conditions the murmur is usually found in conjunction with tachycardia, a forcibly beating heart, and an extension of the area of cardiac impulse towards the left. It is the association with phenomena of this kind which makes the murmur so common in insurance cases (1), and no doubt it is also responsible for some of those instances of 'murmur only heard after exertion' which are sometimes, but wrongly, regarded as evidence of organic disease of the heart.

Of my 133 cases, 33 had definite tuberculous disease of the lungs; in 19 it was early, in 2 it was moderate, in 12 it was advanced. In 16 other cases there was reason to suspect pulmonary tuberculosis. In two-thirds of the cases in which the point was noticed, the tuberculous disease was principally or exclusively at the right apex; in two of these the bruit was heard to the right of the sternum only, a most unusual circumstance. These murmurs occurred (in my out-patient room at the Bristol General Hospital) in about 10 per cent. of all cases of phthisis, without special incidence at any particular stage of the disease. Such sounds are sometimes described and classified as a form of interrupted air entry or cog-wheel breathing, and though, of course, they differ from the interrupted air entry which is heard in the immediate neighbourhood of tuberculous lesions of the lung, they have some diagnostic value. In several cases the discovery of a cardio-respiratory bruit of this type has led me to a search for direct signs of pulmonary tuberculosis, and has thus helped materially in early diagnosis.

The manner in which cardio-respiratory murmurs are produced has been the subject of much discussion. The arguments I shall bring forward apply mainly to the bruit heard in cases belonging to Group II; probably, however, the hypothesis supported with regard to these cases is equally applicable to the rest. My observations lead me to agreement with the friction theory upheld by Dr. Thomas Lewis in a recently published paper (2). The bruit is, I believe, caused

by friction between the pleural surfaces, produced during the inspiratory expansion as a rule, and accentuated to the point of audibility by the impact of the ventricles in systole.   The evidence is briefly as follows :—

(*a*) Certain of the inspiratory-systolic bruits have a coarse, grating character such as could only be produced by attrition.   Between these and the commoner, softer bruits, a perfect gradation of types is found.

(*b*) In several cases, a rasping, inspiratory-systolic rub at one point has been associated with a bruit of the more characteristic whiffing type at another spot ; in others the bruit is distinctly frictionary in one posture but whiffing in another.

(*c*) In 19 of the 133 cases displaying this kind of murmur, there was distinct evidence of recent or old pleurisy, usually in the same area as that of the murmur, which in several instances was identical in character with a pleuritic rub heard on the same side of the chest, differing from it only in localization and rhythm.

(*d*) In 13 of the 133 cases of cardio-respiratory murmur, subclavian murmurs were heard.   These are always inspiratory-systolic in time, and they further resemble the cardio-respiratory murmur in their brevity and in their abrupt arrival and disappearance.   For such murmurs an alveolar origin is inconceivable : they are almost certainly due to friction.

(*e*) The very character of the bruit (its loudness, its sudden beginning, brief career, and abrupt end) suggests the brushing together of two surfaces rather than the passage of air into or out of the alveoli.

(*f*) The bruit is abolished when the pleura is fixed in deep inspiration.

These points, added together, make a good case for the belief that in many instances the origin of the bruit is to be sought in pleural friction.   If this be admitted for some of the cases, it must probably be held to apply to all ; for the bruit has so characteristic an individuality that anything which explains its occurrence in some is probably responsible for all.   Lesions of the pleura are so common, and so often latent as far as clinical signs are concerned, that there is no reason to shrink from such a generalization as this, even without bringing in the quite plausible argument that the friction of the normal pleural surfaces pressed together by some abnormal force might conceivably produce an abnormal sound.

In conclusion, the following points seem to be of practical value in connexion with cardio-respiratory murmurs :—

1. The need for distinguishing them from organic intra-cardiac murmurs, and the means to be used to this end.

2. The association of the first type with pulmonary collapse, and of the second type with tuberculosis of the lungs and nervous excitement.

3. The probability that, in the second group at any rate, the murmur is a peculiar type of friction sound.

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PRIMARY OCCLUSION OF THE OSTIA OF THE HEPATIC VEINS

By THEODORE THOMPSON AND HUBERT M. TURNBULL

(From the Pathological Institute of the London Hospital)

With Plate 15

OBSTRUCTION to the hepatic veins, sufficient to cause the appearance of symptoms and to lead to a fatal termination, is a rare pathological condition. The symptoms have usually appeared in persons who were apparently in good health. In general, it may be said that the symptoms are those of portal obstruction associated with, and in many cases overshadowed by, hepatic insufficiency. The cases may, however, be divided into two clinical types. In one the morbid manifestations appear gradually and the illness lasts from one to six months. Epigastric pain is usually a premonitory symptom and the patients are often treated for indigestion in the earlier stages. Ascites then develops and persists in spite of repeated paracentesis abdominis. Enlargement of the liver can usually be detected, and the organ is tender to palpation. The veins upon the belly and chest become dilated. Vomiting is frequently present. Cyanosis has been observed in many cases, although the heart gave no indication of dilatation. Haematemesis is rare. Jaundice occurred in only one of the cases to which reference is given at the end of this paper. Ultimately coma and death result from hepatic insufficiency. In the second type of case the symptoms develop with great rapidity and death supervenes in a few days. The abdomen fills rapidly with fluid, and the patient suddenly becomes delirious and comatose. Obscure epigastric pains may have been experienced for some time before the onset of these symptoms. The two cases reported in this paper are examples of these two clinical types. The anatomical changes found therein afford an explanation of the diversity in the clinical course.

The possibility of recognizing the condition during life is a remote one. In those cases in which the condition develops gradually a differentiation from cirrhosis of the liver is extremely difficult. Careful examination of the liver itself may be of assistance. In obstruction of the hepatic veins the enlarged liver is markedly tender on palpation and the edge of the liver is smooth and rounded. In cirrhosis of the liver, on the other hand, the liver is usually not markedly tender and its edge is sharp and hard. The absence of the usual causes of cirrhosis, for instance alcoholism and syphilis, might perhaps be of

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some value as a point in the differential diagnosis. The differentiation of
obstruction to the hepatic veins from obstruction to the inferior vena cava may
be made by examination of the current of blood in the collateral circulation.
An upward direction of the current would indicate that the inferior vena cava
was obstructed, a downward direction would indicate that the obstruction was
confined to the hepatic veins. In tuberculous peritonitis with ascites there will
be signs of peritoneal inflammation, and specific evidence of tuberculous infection
may be obtained. Diffuse carcinomatosis of the peritoneum with ascites may
be distinguished by signs of the primary growth or by the presence of
secondaries, for instance enlarged glands in the left supra-clavicular fossa.
It is, however, probable that a correct diagnosis could be made rarely during
life in this type of case, and then only by a process of exclusion of the more
common causes of ascites. In the more rapid cases the association of cyanosis
with an enlarged, tender liver and ascites makes a clinical picture which closely
resembles myocardial failure. The resemblance is usually accentuated by
marked congestion of the lungs. Oedema of the legs may, however, be absent
and afford the clue to the correct diagnosis.

     At the autopsy the remarkable association of a liver showing extreme
atrophy from venous congestion with a heart in which there is no evidence
of chronic embarrassment immediately suggests the site of the lesion.

     Examination of the literature shows that obstruction of the hepatic veins
may be caused by a variety of conditions.   It is, unfortunately, impossible
to determine the condition which was present in all the reported cases owing to
the incompleteness of many of the anatomical descriptions. In some cases,
indeed—for instance, a case of Cohn (4) and three cases of Quincke (16)—the site
and nature of the obstruction have not even been mentioned. The hepatic
veins in some part of their course within the liver may be obstructed by the
pressure of hydatid cysts (Rolleston (18)), by involvement in tumours, granulo-
matous or cicatricial tissue (Barlow (1)), or by thrombosis (Schüppel (20),
Umbreit (22)). Stenosis or complete occlusion of the orifices of the hepatic veins
is a rarer condition. In a case of Fagge (6), the orifice of one hepatic vein was
greatly constricted by a gumma; in cases of Wilks (24) and West (23), the
orifices together with the inferior vena cava were involved in gummata.
Rolleston (17) has described a case of thrombosis of the orifice of the right
hepatic vein with an independent, parietal thrombus in the inferior vena cava;
Fisher (7) a case of complete obstruction of the orifices of both hepatic veins
by thrombosis; Willcocks (25) and Sternberg (21) cases of thrombosis of the
inferior vena cava with consequent obstruction of the orifices of the hepatic
veins.   In several cases (Frerichs (8), Rosenblatt (19), Gee (9), Hainski (10),
Kelynack (11), Churton (3)), constriction, or complete obliteration, of one or
more orifices was ascribed to involvement in inflammation spreading from the
surrounding tissues.

     Three cases of obstruction at the orifices, due to a condition apparently

distinct from any of those mentioned above, were described by Chiari (2). In these the stenosis, or obliteration, was due to a thickening of the intima. The condition was quite independent of changes in the surrounding tissue and was considered by Chiari to be a disease *sui generis*. In his first case the disease was found in a woman of 28, in his second in a woman of 59, and in his third in a man of 29. Similar cases have since been described by Lichtenstern (13) (male, aged 20), Craven Moore (5) (female, aged 25), Penkert (15) (male child, aged 22 months), and Kretz (12) (sex and age not mentioned). The term 'primary' may be applied to the obstruction at the ostia in this group of cases in order to indicate that the condition was not the result of changes in the surrounding tissues.

The case of Fisher (girl, aged 3) should apparently be included in this group. So far as can be judged from the description, it appears to differ only in the interpretation of the changes which was put forward by the author. In a case of Osler (14) (male, aged 24) the orifices of the right and left hepatic veins were greatly narrowed, as in many of the cases of the group defined by Chiari, but in addition the inferior vena cava from the orifices of these veins to the entrance of the left renal vein was represented by a dense fibrous cord. This case may be an example of the group defined by Chiari, complicated by thrombosis of the inferior vena cava, or it may represent a late stage of the condition described by Sternberg. There is little doubt that the majority of the cases reported by Frerichs, Rosenblatt, Gee, Hainski, Kelynack, and Churton were similar to those of Chiari. In the absence of a description of the histological changes at the ostia of the veins, this is impossible to decide, but the evidence put forward by the authors in favour of the view that the occlusion was secondary to external inflammation is not conclusive. Two cases are reported by Frerichs. In one (Observation XX, female, aged 38), there appears to have been extensive fibrosis of the liver, and the changes in the veins may have been secondary. The figures illustrating the second case, however (Observation LXII, male, aged 45, Tafel XIII), show a condition at the orifices of the veins similar to that described by Chiari. In Rosenblatt's case (male, aged 27) the occlusion of the orifices was considered to be secondary because the periphery of the left lobe of the liver was cirrhotic and firmly bound to the abdominal wall, whilst many strands of connective tissue passed from the capsule into the parenchyma. In this case there was also a carcinoma of the size of a goose's egg in the right lobe of the liver with secondary nodules in the peritoneum. In Gee's case (male child, aged 17 months), the ostia were occluded by 'thin membranes'. The liver showed the changes typical of venous obstruction. In addition the capsule of the liver was thickened everywhere, but especially about the suspensory ligament and the edge of the left lobe. There was also thickening of the capsule of Glisson in the portal fissure and canals. Unfortunately, there is no description of the microscopic changes. Hainski and Kelynack considered that the occlusion of the orifices of the veins in their cases was secondary to an inflammation spreading from the capsule of the liver. In Hainski's case (female, aged 22), the suspensory ligament and capsule of the liver and the whole of the parietal peritoneum were thickened. In Kelynack's case (female, aged 32) there were firm, fibrous adhesions between the liver and the diaphragm and in the neighbourhood of the inferior vena cava. There were also slight pelvic adhesions. The perihepatitis and peritoneal adhesions in these cases may well have been a secondary phenomenon; in both cases the abdomen was greatly distended by ascites. Unfortunately there is no microscopic description of the orifices of the hepatic veins. In Churton's case

(male, aged 26), an hepatic vein in the centre of the liver contained an old, whitish clot, whilst the mouth of the vein into the inferior vena cava was very narrow and completely blocked by whitish clot. There was a diffuse, intercellular fibrosis throughout the liver. In the microscopic report it is stated that 'the thrombi are in some parts adherent to, or rather fused with, the wall of the vein and the connective tissue beyond, as though the connective tissue had invaded the vein and projected into it.'

The following two cases are additional examples of the condition which was described by Chiari :—

Case I. Rosina T., a married woman, aged 26. Admitted to the London Hospital on September 16, 1910. Died October 8, 1910.

Clinical history. The patient had enjoyed excellent health until the last five months. She then began to experience pains in the abdomen, especially on walking. A month later her abdomen began to swell and she consulted a doctor, who told her she was pregnant. The swelling of the abdomen greatly increased and she passed very little urine. Loss of appetite and weakness appeared, and for fourteen days before admission she had wasted. Her health had been good except for the usual childish complaints and the catamenia had always appeared regularly until the last few months. The only point of interest in the family history was that her father died of pulmonary tuberculosis.

On examination, the patient looked ill. The temperature was continuously subnormal, 97·5° F. The rate of respirations was 24, and of the pulse 105. The face and arms had a peculiar heliotrope colour. The limbs were much wasted. The abdomen was greatly enlarged and showed distended veins. There was a marked fluid thrill and shifting dullness in the flanks, indicating a considerable amount of ascites. The legs were much swollen, but no abnormal physical signs were detected in the heart or lungs. Nothing abnormal was detected on vaginal or rectal examination. On September 19, 1910, paracentesis abdominis was performed and thirty-three pints of clear ascitic fluid were removed. After this operation the liver could be felt to be enlarged: it extended 1½ inches below the costal margin and had a hard well-defined edge. Examination of the ascitic fluid showed numerous cells; the majority of these were endothelial, a few were small lymphocytes. The diagnosis was thought to lie between cirrhosis of the liver, malignant disease, and tuberculous peritonitis. The fluid rapidly reaccumulated in the abdomen, and on September 25 ten pints were removed. About twenty ounces of urine were passed daily; this was of high specific gravity and free from albumin or other abnormal constituents. On Oct. 5, 1910, she was transferred to Mr. Jonathan Hutchinson, jun., and laparotomy was performed. An incision was made in the middle line and about two pints of straw-coloured fluid escaped. The spleen was felt to be large and firm. The liver was slightly enlarged and firmer than normal. It contained neither gummata nor malignant deposits, nor was there any evidence of cirrhosis. The veins in the falciform ligament were much enlarged, and the peritoneum was normal. Omentopexy was performed, the great omentum being stitched into the anterior abdominal wall. A diagnosis of Banti's disease was suggested, but the absence of anaemia seemed to be against this supposition. The patient recovered well from the anaesthetic, but two days after the operation she became restless and then sank into a comatose condition. The breath smelt of acetone. Large doses of alkalis were given and pituitary extract injected, but the breathing became more laboured, the cyanosis increased, and she died on Oct. 8, the third day after the operation.

Summary of Autopsy.   P. M. 944.   1910.   October 10.

'*Heart failure.   Organizing thrombosis of splenic vein and portal vein at junction with splenic.   Thrombi on walls of large intrahepatic portal veins. Occlusion of the distal extremities of the hepatic veins.   Diaphragmatic constriction in hepatic portion of inferior vena cava.   Operation: laparotomy; suture of omentum to parietal peritoneum.   Distension by fluid blood or postmortem clot of inferior vena cava below constriction, and of superior and inferior mesenteric and iliac veins.   Varicose veins in oesophagus.   Severe back-pressure atrophy of liver (3 lb. 5 oz.), with small regeneration nodules. Back-pressure kidneys (13½ oz.).   Enlarged, engorged spleen (1 lb. 4 oz.). Great congestion of mucosa of stomach, intestines, bladder, and uterus.   Great ascites.   Foramen ovale closed.   Distension of right heart.   Petechiae in pericardium of posterior surface of right ventricle.   No pulmonary embolism. Great congestion of lungs.   Pressure collapse of lower borders of both lungs and of posterior part of right middle lobe.   Very slight fatty atheroma confined to the commissure of the aorta and the aortic flap of the mitral valve.   A few minute fat-necroses on surface of pancreas.   Follicular cysts in atrophic ovaries.   Oedema of legs.   Extreme cyanosis of face, shoulders, and hands.   Examination of brain not permitted.*'

The lower border of the liver extended from the tip of the ninth costal cartilage on the right side to the eighth on the left.   There was a band of fibrous adhesion passing from the under surface of the liver, close to the right border, to the hepatic flexure of the colon.   The liver appeared to be of normal size. The Spigelian lobe ended in a free, pear-shaped mass below the level of the caudate lobe.   The whole liver felt firmer than normal.   Its surface was roughened, resembling morocco leather; on the inferior surface there were many raised nodules of the size of a pin's head.   The capsule was slightly more opaque than normal.   On section blood flowed spontaneously.   The cut surface of the right lobe showed a network of sunken, deep red lines enclosing slightly raised brown areas about the size of a pin's head.   In the centres of these areas were portal systems.   The cut surface of the left lobe and the Spigelian lobe was deep red and sunken, with very small, slightly raised grey nodules, in the centres of which were portal systems.   The consistency of the left lobe was firmer than that of the right.

In the hepatic portion of the inferior vena cava there was, at the level of the upper border of the Spigelian lobe, a diaphragmatic constriction showing an aperture 4 mm. in diameter.   On looking down through the cardiac opening of the inferior vena cava this aperture was seen to lie in the floor of a rounded cavity.   The cavity showed two shallow concavities, one on the left, the other on the right, and both slightly anterior to the aperture.   These evidently corresponded to the large left and right hepatic veins.   The largest was on the left side, above the upper border of the Spigelian lobe.   It was about 1½ cm. in diameter.   In the left extremity of its floor there were two minute, shallow, funnel-shaped apertures, through which a very fine probe could be passed.   Sections through these apertures revealed fibrotic cords corresponding to the large radicles of the left hepatic vein.   In the smaller right concavity no aperture was visible, but section revealed a fibrotic cord passing into the right lobe.

In the portion of the vena cava below the constriction there were several minute dimples or small white slightly raised nodules which corresponded to

the orifices of narrowed or completely obliterated hepatic veins. Through these orifices a probe could not be passed. There were also three apertures which admitted a probe. The corresponding venules passed into the retroperitoneal areolar tissue.

On the left margin of the inferior vena cava, immediately below the diaphragmatic constriction, there was a raised plaque of grey colour about 3 cm. long and $\frac{1}{2}$ cm. broad.

Sections through the liver in the neighbourhood of the vena cava showed that the large tributaries were represented by fibrotic cords for a distance of from $\frac{1}{2}$ inch to $2\frac{1}{2}$ inches. These solid cords usually terminated abruptly at the confluence of two branches.

The veins on the inferior surface of the diaphragm in the neighbourhood of the liver were rather more numerous and more prominent than usual. The umbilical vein was replaced by a fibro-lipomatous cord. No enlarged parumbilical veins were noted. There was no ductus venosus.

Microscopic Appearances.

(1) *Serial longitudinal sections through an obliterated vein which entered the concavity representing the left main hepatic vein (vide* Plate 15, Fig. 1). The obliterated vein is formed by the confluence of two large veins which converge at an obtuse angle. The obliterated vein has an adventitia in which there are some large nerves and many veins and capillaries, which are dilated and engorged. Internal to this there is a stout muscularis which is bounded internally by an elastic lamina. There appears to be a little fibrosis of the innermost part of the muscularis on one side of the ostium. Within the elastic lamina is a vascularized tissue which completely fills the lumen. This tissue has a matrix of collagen fibres, which are stained deep red by van Gieson's method. Scattered amongst these are considerable numbers of fine elastic fibrils. There are relatively few cells. The cells are of elongated spindle shape. There are some small areas of haemorrhage, but no pigment. The tissue contains many capillaries and a few arterioles. The arterioles have a well-developed muscularis. The largest capillary space runs longitudinally. It is formed by the junction of the two large veins and can be traced into the funnel-shaped depression on the surface. It lies to one side of the centre of the lumen.

The tissue in the lumen of the obliterated vein merges with a slight thickening of the intima of the left hepatic vein. This thickening surrounds the orifice of the obliterated vein, disappearing rapidly on one side of the orifice, less rapidly on the other. In structure it is less dense than the tissue within the lumen of the vein. At its lower end the fibrous tissue in the obliterated vein terminates abruptly in the intima of the two large, converging tributaries. It thus resembles a fibrous plug with an arched lower border, the concavity of which is directed towards the spur formed by the junction of the two tributaries. The two tributaries have a wide lumen. Their intima is slightly thickened, consisting of a very delicate connective tissue in which there are very few fine elastic fibrils. This intimal thickening is continuous with a zone of similar tissue upon the arched lower border of the fibrous plug and with a thickening of the intima in some of the largest of the capillary spaces within the plug. There is a sharp demarcation between this layer of delicate connective tissue and the dense tissue of the fibrous plug.

Other, smaller, tributary veins pass from the liver to the wall of the obliterated vein. Some of these remain wide until close to the wall, when they are suddenly narrowed and their lumen is filled by canalized tissue. In others the intima is thickened for a considerable distance before the lumen is obliterated. The tissue blocking the lumen of these veins differs from that within the main vein in that it contains finer collagen fibres and usually no elastic. Some

of the canals in these veins can be traced into capillary spaces within the lumen of the main vein; others appear to enter the dilated veins in the adventitia.

(2) *Transverse and longitudinal serial sections of other obliterated veins, taken at distances of from half an inch to two inches from the inferior vena cava.* These vessels have an adventitia in which there are nerves, and a muscularis which is bounded by an internal elastic lamina. Within this elastic lamina the lumen is filled by a tissue similar to that which has been described in the main vein in section 1. Elastic fibrils are as a rule less numerous. The tissue is canalized by many capillaries of varying size. Tributaries pass into these veins. Before entering the wall the tributaries become narrowed and their lumina are filled by canalized tissue. At a short distance from the wall the large tributaries usually have a wide lumen and only a moderate thickening of the intima. Many of the small veins, on the other hand, are filled by canalized tissue to a considerable distance from the wall. The tissue within the lumina of the tributaries is less fibrous than that within the main veins.

(3) *Longitudinal section through the inferior vena cava at the site of the constriction.* The constriction is formed by a localized, projecting, triangular thickening of the intima, internal to the elastic lamina. The intimal thickening consists of collagen and fine elastic fibrils with relatively few elongated spindle cells. It contains numerous capillaries. It is similar in structure, therefore, to the tissue which fills the lumina of the obliterated veins. There is no abnormality in the adventitia and muscularis save that the vessels in the former are dilated.

(4) *Transverse section of inferior vena cava at the site of the grey plaque.* The veins and capillaries in the adventitia are numerous, large, and engorged. There is no fibrosis of the media. The plaque is formed by a local thickening of the intima. Its summit is flat, its borders rise abruptly. In structure it resembles the tissue which fills the large obliterated veins save that it is less dense and more cellular. It has a stroma in which there are numerous collagen fibrils, a few very fine, short, elastic fibrils, and considerable numbers of spindle cells. There are also, especially in the internal layers, small collections of lymphocytes and larger mononuclear cells. There are a very few cells which contain granules of yellow pigment. It contains numerous capillaries and a few arterioles.

To one side of the plaque, and passing for a short distance beneath it, there is a slight thickening of the intima of different structure. This contains numerous, well-developed elastic fibres and is not vascular. There is a sharp demarcation between this thickening and that which forms the plaque.

On the surface of the plaque and on the adjacent intima there are some large masses of small, oval, Gram-negative cocci. Beneath these there is no inflammatory reaction.

(5) *Section through the thrombosed splenic vein.* The vessels in the adventitia and muscularis are engorged. There is a slight infiltration of these coats by mononuclear tissue cells. The internal limiting elastic membrane is well preserved. Internal to it there are some small, fusiform thickenings of the intima. These are formed by a tissue containing fine collagenous and elastic fibrils and elongated spindle cells. A mass of red thrombus rests upon the intima. The main portion of the thrombus consists of a net of delicate filaments of fibrin (Weigert Gram stain) enclosing red corpuscles. Next the intima there is a zone in which the fibrin is almost entirely replaced by spindle fibroblasts and primitive capillaries. The thrombus is therefore undergoing organization.

(6) *Sections from the surface of the right and left lobes and from the centre of the liver.* In the right lobe of the liver there is a very extensive atrophy of the parenchyma in the centres of the lobules. The areas of atrophy in adjacent

lobules are in continuity, so that the parenchyma is confined to a zone which lies round the portal systems. The atrophied area may extend right up to the portal system. In places there is a little portal fibrosis, adjacent portal sheaths being united to one another. The amount of interstitial increase in the atrophied areas is remarkable. The capillaries therein are separated by broad strands of a fibrous tissue which contains collagen fibrils, considerable numbers of spindle nuclei, and a few fine elastic fibrils. In this fibrous tissue there are also branching chains of epithelial cells. The cells are small and often of flattened, cubical shape. They are arranged frequently in a double row so that they resemble pseudo bile canaliculi closely. The protoplasm is as a rule more abundant than in the cells of the pseudo bile canaliculi of a portal fibrosis. These branching chains of cells are often in direct continuity with the large hepatic cells which lie round the portal systems. They are evidently processes of regenerating hepatic cells. The parenchyma round the portal systems frequently shows further evidence of regeneration, being in the form of small nodules in which the columns of cells have an approximately concentric arrangement. One large hepatic vein shows a slight thickening of the intima.

The section from the centre of the liver has a similar appearance. In the left lobe the atrophy is even more extensive. In many of the atrophic areas there is much haemorrhage. The fibrosis of the atrophied areas is considerably greater than that which is usually found in cases of chronic heart failure, but is less than that of the right lobe. The majority of the atrophied areas are occupied to a much greater extent by distended capillaries, the tissue between the capillaries being much less abundant and containing fewer collagen fibrils. Further, there are no elastic fibrils. Columns of regenerating hepatic cells are confined to a few areas in which the fibrosis is almost as great as in the right lobe. There is no portal fibrosis. The parenchyma round the portal systems is frequently arranged in the form of regenerating nodules. In the larger veins the intima is thickened. The thickening consists of a delicate tissue which contains a very few spindle cells and fine fibrils, stained as a rule yellow by van Gieson's method.

The parenchyma in the sections made for the examination of the obliterated veins (*vide supra*, (1) and (2)) shows similar atrophy and fibrosis. In these sections there is a large portal vein which contains recent mixed thrombus.

(7) *The spleen.* There is no thickening of the capsule or trabeculae. The Malpighian bodies are fairly numerous and of medium size. They contain lymphocytes of normal appearance. The capillary veins in the pulp are greatly engorged. The reticulum of the pulp contains very few free cells; its fibrils are rather more conspicuous than usual, but there is no appreciable increase in the number of fixed cells.

Case II. Florence Louisa H., a married woman, aged 30. Admitted to the London Hospital on October 31, 1910. Died, November 1, 1910.

Clinical history. The friends of the patient stated that four days before admission she became light-headed and then unconscious and had since remained in that condition.

They also stated that she had been attending University College Hospital for indigestion. On inquiry it was found that she had been attending under the Casualty Medical Officer and no notes of her condition could be traced.

On examination her temperature was found to be 97° F. The rate of respiration was 30; of the pulse 120. She was comatose and deeply cyanosed. The pupils reacted to light and were of moderate size. The breathing was noisy and stertorous and crepitations were present. The heart was normal. The liver was enlarged and the abdomen was greatly distended by fluid. There was some oedema of the legs. She did not recover consciousness and died a few hours after admission.

Summary of Autopsy.   P.M. 1019.   1910.   November 1.

Occlusion of ostia of hepatic tributaries of the inferior vena cava. Dia-phragmatic constriction in hepatic portion of inferior vena cava. Extreme congestion and back-pressure atrophy of liver (4 lb. 4 oz.). Great ascites. Slight opacity of peritoneum. Moderately enlarged, congested spleen (9¼ oz.). Extreme engorgement of lungs. Delicate fibrous adhesions in posterior part of right pleura. Slight congestion of kidneys (10 oz.). Petechiae in anterior mediastinum. Heart (9 oz.). Foramen ovale closed. Very slight atheroma; a few pin-point fatty flecks in intima of abdominal aorta. Oedema of pancreas. Extreme cyanosis of face and arms. Brain (2 lb. 14 oz.). No otitis media. No oedema of legs.

The liver was large and its borders somewhat rounded. The Spigelian lobe was small. The capsule was thin. The surface was slightly uneven owing to minute linear depressions, which were most numerous near the antero-inferior border. There were three large veins in the capsule on the posterior surface of left extremity. On section blood flowed spontaneously. The cut surface was of a deep red colour and was beset with small, slightly raised, closely set, pale pin-head areas corresponding in position to portal systems. The large portal systems were conspicuous, the portal veins being dilated. The walls of the larger hepatic veins appeared to be thickened. Fine catheters and probes could be passed along the larger hepatic veins until immediately beneath the inferior vena cava. They could not be passed into the inferior vena cava.

The orifice of the inferior vena cava in the diaphragm was about 2½ cm. in diameter. Viewed through this orifice the portion of the cava above the level of the upper border of the Spigelian lobe appeared as a cavity with concave floor. In the floor, opposite the right border of the Spigelian lobe, there was a round aperture 8 mm. in diameter, which led into the inferior portion of the vena cava. In front, and to the left and right, of this aperture there were two shallow concavities in the floor which corresponded in position to the left and right hepatic veins.

There was a minute grey nodule in the left concavity. On section this was found to correspond to the obliterated ostium of a large vein. There was no visible narrowing of this vein, but across its ostium there stretched a fibrous disk, which was about 3 mm. in depth.

Viewed from below, the cava had a diameter of 2¼ cm. At the level of the upper border of the Spigelian lobe it was narrowed by a diaphragm, in the centre of which lay the aperture described above. For about 2 cm. below this diaphragmatic constriction the intimal surface was slightly nodular and irregular. In the portion of the cava below the constriction there were three small apertures which were of normal appearance and which admitted a probe. Two of these led into small veins in the retroperitoneal areolar tissue on the right of the cava. The third led into a vein in the lower part of the Spigelian lobe. The other ostia were impervious to a probe and were represented by minute dimples or slightly raised white or yellowish-white nodules. The largest of these nodules lay on the anterior surface 5 cm. below the constriction. A section through this revealed a wide hepatic vein. The ostium of the vein was filled by the white nodule, and from the under surface of this there hung a plug of red thrombus 4 mm. long.

There was a rich anastomosis of veins on both surfaces of the diaphragm. The majority of these were of the diameter of No. 18 linen carpet thread; one was very much wider. The ductus venosus was not recognizable. The umbilical vein was represented by a fibrous cord embedded in fat.

Microscopic Appearances.

(1) *Serial longitudinal sections through the tributary entering the left hepatic vein* (*vide* Plate 15, Fig. 2). In the adventitia of the hepatic vein the capillaries and veins are dilated. There appears to be some fibrosis of the adventitia and muscularis of the hepatic vein on one side of the ostium and the muscularis here is infiltrated by considerable numbers of lymphocytes. The muscularis of the hepatic vein and the tributary is bounded by an internal elastic lamina. The ostium of the tributary is completely filled by a disk of tissue which lies internal to the elastic lamina. The surface of the disk which is directed towards the left hepatic vein is almost flat; the surface which is directed towards the tributary vein is concave. The tissue merges with the intima of the hepatic and the tributary vein. The intima of the hepatic vein rapidly attains its normal thickness; that of the tributary vein is thickened throughout the section. The tissue of the disk is very similar in structure to that which filled the lumen of the large veins in Case I. The stroma contains closely packed collagen fibres, which are stained deep red by van Gieson's method, and considerable numbers of very fine elastic fibrils. It contains, in addition to spindle cells, small groups of lymphocytes, considerable numbers of eosinophil leucocytes, and a few plasma cells. Pigment granules are not present.

The border of the disk which is directed towards the tributary vein is of much less dense structure, having only a few fibrils which are stained red in van Gieson. The thickening of the intima of the tributary vein also consists of this delicate connective tissue. There is, however, no sharp line of differentiation between the dense and delicate tissue. The disk contains capillaries and is perforated by numerous large canals which pass from the tributary to the left hepatic vein. The ostium of the tributary appears, therefore, to be. bridged by a cribriform plate of fibrous tissue which is derived from the intima. In some of the canals there is organizing thrombus. Some of the smaller hepatic veins in the surrounding parenchyma are completely filled by canalized tissue. This tissue contains only a few fibrils which are stained red by van Gieson's method, and very few fine elastic fibrils.

(2) *Longitudinal section through the orifice of a small hepatic vein opening into the lower part of the vena cava* (*vide* Plate 15, Fig. 3). The muscularis of the veins is bounded by an internal elastic lamina. The intima round the orifice is thickened to form a triangular projection, the upper surface of which lies in the plane of the vena cava. The space between the intimal projections is occupied by a plug of thrombus. This has one flat surface which lies in the same plane as the inner surface of the vena cava. Its other extremity hangs downwards in the lumen of the hepatic vein. The tissue which forms the intimal thickening contains spindle cells and is infiltrated by lymphocytes, eosinophil leucocytes, and plasma cells. There are many capillaries in it. In its external parts there are numerous collagen fibrils which are stained red by van Gieson's method, and a few fine elastic fibrils. Towards the centre it becomes more delicate, containing very few fibrils which are stained by van Gieson's method and no elastic fibrils. It then merges with the thrombus, which is almost completely organized in its upper part. The dependent portion of the thrombus is not organized and consists of red corpuscles entangled in a net of fibrin. At a considerable distance from the ostium the intima of the hepatic vein becomes diffusely thickened. This thickening consists of a delicate tissue in which there are some fine elastic fibrils, but no fibrils stained red by van Gieson's method. It is not vascularized. There is a thickening of the intima of similar structure in a large radicle of the hepatic vein.

There is no abnormality in the adventitia and muscularis. The surrounding hepatic parenchyma is extensively destroyed by venous congestion. It shows

some small areas of fibrosis, beneath the adventitia of the hepatic vein, at a considerable distance from the ostium.

(3) *Transverse sections through the constriction in the inferior vena cava.* The constriction is formed by a triangular spur of thickened intima, beneath which the internal elastic lamina is intact. The tissue which forms the thickening contains closely set collagen fibrils which are stained red by van Gieson's method. It also contains considerable numbers of fine elastic fibrils. In addition to spindle cells there are considerable numbers of lymphocytes and eosinophil leucocytes and some plasma cells. It contains numerous well-formed capillaries. There are small areas of haemorrhage, but no collections of pigment. The muscularis and adventitia show no abnormality.

(4) *Sections of the hepatic parenchyma.* In some of the large hepatic veins the intima is markedly thickened. The thickening consists of a delicate fibrillar tissue containing relatively few spindle cells. It contains collagen fibrils which are stained yellow by van Gieson's method, and numerous fine elastic fibrils. Some of the small hepatic veins are almost closed by a similar thickening of the intima. In the large portal veins there are some small local thickenings of the intima, rich in fine elastic fibrils. One large hepatic artery shows a slight thickening of the intima with reduplication of the internal elastic lamina.

There is complete destruction by haemorrhage of the parenchyma save for a narrow zone of cells round the portal systems. The walls of the central veins have in most cases been torn asunder; the walls are slightly thickened, and occasionally there is some thickening of the 'trellis fibrils' which radiate from them. There are no regeneration nodules.

(5) *The spleen.* There is no thickening of the capsule and the trabeculae. The intima of the larger arteries is slightly thickened by reduplication of the internal elastic lamina. The Malpighian bodies are numerous and well formed. The pulp is greatly engorged. The reticulum of the pulp contains relatively few free cells. It shows no increase of fibrils in van Gieson's stain.

(6) *The pancreas.* There is a little thickening of the intima, containing fine elastic fibrils, in the largest interlobar vein, and a small area of elastic reduplication in the intima of the corresponding artery. The lobes are separated by broad lipomatous septa, and a few fat cells are present in the intralobular septa. The islands are numerous and well formed. There is a little digestion of the acini in the periphery of the lobes and there are a few small areas within the lobules in which the cells of the acini are dissociated, pale, granular, and stained entirely by eosin.

Summary and Interpretation of Pathological Changes.

In both Case I and Case II the primary pathological condition appears to be occlusion of the orifices of the hepatic veins at their entrance into the inferior vena cava, accompanied by partial obstruction of the inferior vena cava immediately below the entrance of the large right and left veins. Secondary to this there is back-pressure atrophy of the liver, enlargement and engorgement of the spleen, and great ascites. This is accompanied in Case I by oedema of the legs. In this case there is also a thrombus, which is undergoing organization, in the splenic vein and in the portal at its junction with the splenic. This thrombosis is evidently a terminal affection and doubtless secondary to the obstruction of the hepatic veins. The destruction of the liver by the venous obstruction is in both cases extreme. In Case I there is a remarkable fibrosis of the atrophied areas. The fibrous tissue approximates in density to that of

a portal fibrosis and contains some elastic fibrils. There is also considerable regeneration of the parenchyma in the form of nodules at the side of the portal systems and of pseudo bile canaliculi in the fibrotic central areas. In Case II there is hardly any trace of fibrosis and there is no regeneration. In Case I the spleen is much larger than in Case II, and there is a slight fibrosis of the pulp which is not present in Case II.

In both cases the orifices of the large hepatic veins are occluded by vascular, canalized fibrous tissue. The fibrous tissue is dense, containing numerous collagen fibres and some fine elastic fibrils. The plugs of fibrous tissue end abruptly at the ostia and almost as abruptly in the hepatic veins. In the latter they merge into a thickening of the intima, of less dense structure, which extends for a variable distance. The intima of the tributaries of the occluded veins is usually thickened or the lumen is entirely filled by canalized tissue. The tissue forming the thickening of the intima or occluding these tributary veins is less dense than that which occludes the main vessels. The two cases differ widely in the extent to which the lumen of the main veins is occluded. In Case I the tissue extends for from half an inch to two and a half inches from the vena cava. In Case II the tissue merely forms a cribriform plate across the ostia of the large veins. In this case one of the hepatic veins which opened into the lower part of the inferior vena cava is occluded in a different manner. In place of a plate of dense fibrous tissue there is a projecting thickening of the intima which merges into a central, organizing thrombus.

In Case I the extensive fibrosis and the abundant regeneration in the liver, the great enlargement and slight fibrosis of the spleen, indicate that the venous occlusion had been present for a considerable time. The pathological condition has apparently been compatible with life for a considerable period, the extensive destruction of the liver being compensated by regeneration. There is evidence of a recent increase in the destruction of the liver by back-pressure, particularly in the left lobe. There is, however, no evidence of any increase in the occlusion of the ostia of the hepatic veins. The increase in the venous obstruction was doubtless caused by failure of the heart. This, in conjunction with the thrombosis of the splenic and portal veins, would explain the terminal onset of hepatic insufficiency. In Case II the fibrous disk obstructing the tributary of the right vein appears, when judged by its structure, to be of almost as long standing as the fibrous plugs in Case I. But the effects of back-pressure in the liver and spleen are, apparently, much more recent. There is very little fibrosis and no regeneration in the liver; the spleen is much smaller and shows no fibrosis. The escape of the liver and spleen from the effects of back-pressure in the earlier part of the disease is perhaps due in part to the peculiar structure of the original obstructions and in part to the limited number of veins which were then affected. Thus the obstruction caused by narrow disks, perforated by numerous wide canals, was probably less severe than that caused by the extensive plugs of fibrous tissue in Case I with their smaller canals. That all the veins had not been completely obstructed by the original lesion is shown by section 2 (Fig. 3).

In this section a vein which had not been occluded before, or had only been occluded partially, has recently been closed completely by thrombosis. The ultimate destruction of the liver, which caused the sudden onset of symptoms of hepatic insufficiency, can in this case be explained by a terminal increase in the obstruction at the ostia of the veins; organizing thrombus is present not only in the ostium of the vein in section 2 (Fig. 3), but within the canals in the fibrous disk in section 1 (Fig. 2).

The tissue occluding the large veins is in both cases essentially similar in structure. The diaphragmatic projection which in both cases partially occludes the inferior vena cava and the plaque upon the cava in Case I are of the same structure. It would appear, therefore, that all these abnormalities have the same pathogenesis.

In all the lesions the tissue is inflammatory in character. It is rich in vessels and contains only very fine elastic fibrils which have no special arrangement; further, it occasionally contains collections of lymphocytes, eosinophil leucocytes, and plasma cells. The tissue is formed by the intima internal to an intact elastic 'lamina', or more properly 'layer' (elastica interna). The adventitia and muscularis are almost unaffected. The dilatation of the veins and capillaries in the adventitia is obviously the result of the venous obstruction and the establishment of a collateral circulation. There is only a little fibrosis and infiltration of the adventitia and muscularis at the ostium of the occluded vein in Case II, section 1 (Fig. 2). In Case I there is a little fibrosis of the muscularis immediately below the intima on one side of the ostium of the occluded vein. The stimulation to the inflammatory changes has evidently arisen within the lumen. The lesions represent an endophlebitis.

In endophlebitis the intima may become thickened by inflammatory proliferation independent of any deposit of thrombus upon the surface (pure endophlebitis), or the organization of thrombus by the intima may play the chief rôle (thrombophlebitis). In the present cases the character of the tissue, the position of the lesions, and their sharp demarcation are in favour of a thrombophlebitis rather than a pure endophlebitis. The great vascularity of the tissue is such as is seen in thrombophlebitis. The obstruction of the hepatic veins has occurred at their ostia; the tributaries of the large right and left veins are affected in both cases, and the constriction of the vena cava is present immediately below the openings of the large right and left veins. There is no apparent reason why these sites should have been selected by a pure endophlebitis, but these are positions in which thrombosis might be expected. In the selection of a site for thrombosis the important part played by retardation of the blood-stream and alterations in its currents is universally recognized. At the diaphragmatic opening of the inferior vena cava there must frequently be retardation or even reversal of the blood-stream, consequent upon increase of pressure within the thorax. The ostia of veins are positions in which eddies are liable to occur in the blood-stream. Such eddies could also occur at the junction of the converging streams from the large right and left veins with the stream from the inferior

x 2

portion of the vena cava. The lesions are found, therefore, in positions which are favourable for thrombosis. The sharp demarcation and focal nature of the lesions is a prominent feature. It is most conspicuous in the obstruction of the veins in Case II, in the diaphragmatic constriction of the vena cava in both cases, and in the plaque upon the vena cava in Case I. Thus the fibrotic intima in Case II stretches across the ostium as a narrow cribriform plate, with its upper surface flat and in the plane of the vena cava, and with its lower surface arched. The constriction of the vena cava is in both cases formed by a sharp triangular spur of intima, the attached base in Case I being of less dimension than the two free sides. The plaque in Case I also rises abruptly from the intima. Sharply defined projections of the intima of this nature are not seen in ordinary cases of pure endophlebitis. Such projections could be formed by the organization of thrombus which had been silted up at the junction of converging streams of blood.

Although, as indicated above, the ostia of the hepatic veins into the inferior vena cava would appear to be sites which are peculiarly favourable to the formation of thrombi, yet routine examination in the Institute of a very large number of autopsies has shown that the occurrence of such thrombi is of extreme rarity. This is recognized by other observers. The rarity of thrombi in this position may perhaps be explained by the marked obliquity of the entering veins and the diminished coagulability of the hepatic blood (Kretz, 1902). That thrombi may be deposited at the ostia of the hepatic veins is demonstrated by the following case. The case also shows that such thrombi may take the form of sharply defined projections. Further, the thrombi occupy positions identical to those occupied by the fibrous tissue in Cases I and II—in the two largest veins they occur on the orifices of their branches, but in the smaller veins on the orifices into the inferior vena cava.

Case III. Charles T., aged 70. P. M. 250. 1911. March 18.
Summary of Autopsy.

Septicaemia. Pelvic cellulitis. Operation: suprapubic prostatectomy. Slight broncho-pneumonia. Hypertrophy of bladder. Dilatation of ureters and pelves of kidneys (10½ oz.). Haemolytic staining of intima of vessels. Retroperitoneal cysts, lined by stratified ciliated epithelium, between third part of duodenum and pancreas. Meckel's diverticulum. Recent thrombus in orifices of hepatic veins.

The liver weighed 3 lb. 11¾ oz. It was of normal shape. The borders were slightly rounded. The capsule was thin. On section the lobulation was distinct, each lobule having a dark centre and a lighter periphery. The inferior vena cava was examined after the liver had been fixed in formalin. Two large left hepatic veins opened into the cava at the left extremity of the upper border of the Spigelian lobe. In the anterior border of the orifice of the smaller of these there was a semilunar deposit of soft, yellowish thrombus. About 2 cm. from the orifice of the larger the ostia of three tributaries were visible. One of these was partly occluded by a similar semilunar deposit of thrombus. The ostia of the branches of the right hepatic vein were also occluded, the vein being represented by a depression 1 cm. deep which had a concave floor lined by

soft, yellowish clot. There was a large vein from the right lobe of the liver which entered the vena cava $2\frac{1}{2}$ cm. below the level of the upper border of the Spigelian lobe. Its orifice was oval, measuring about $1\frac{1}{2}$ cm. in longest diameter. The anterior half of the lumen of the orifice was filled by a semilunar mass of yellowish thrombus. Vertical section through this vein at its orifice showed that the thrombus projected from the anterior lip like a bracket. It was triangular in shape, with sharp free edge. Its base was attached to the hepatic vein at and immediately below the ostium. Its upper surface was flat and flush with the inner surface of the vena cava; the lower surface sloped towards the inner surface of the hepatic vein. A second large vein from the right lobe entered the vena cava 1 cm. further back. The orifice was free from thrombus. Opposite this a small vein entered from the Spigelian lobe. The edges of its orifice were covered by a slight deposit of thrombus of rusty brown colour.

Microscopic appearances (vide Plate 15, Fig. 4). A vertical section was made through the anterior lip of the hepatic vein which opened into the inferior vena cava $2\frac{1}{2}$ cm. below the level of the upper border of the Spigelian lobe.

The angle at the junction of the hepatic vein and the vena cava is slightly rounded. Upon this angle there is a triangular deposit of thrombus. This appears to rest directly upon the internal elastic lamina. One free surface is in the same plane as the inner surface of the vena cava; the other slopes towards the inner surface of the hepatic vein and is prolonged thereon as a narrow deposit. The thrombus contains filaments of fibrin, but is for the most part granular. It is not stained by Zenker's modification of Weigert's fibrin method. White corpuscles are not present. Red corpuscles are only present in a very few spots and then only in small numbers. In the thrombus, especially in its superficial layers, there are numerous Gram-positive organisms. The majority of these are small diplo- and streptococci, but there are also large diplo- and streptococci and large bacilli. There is no abnormality in the muscularis and adventitia.

Sections of the liver close to the vena cava show that there is congestion of the capillaries in the centres of the lobules. Some of the smaller hepatic veins are lined or filled by granular thrombus. Granular thrombus is also seen upon the walls of some of the portal veins.

Consequently it appears justifiable to conclude that the occlusion of the hepatic veins in Cases I and II is the result of a thrombophlebitis which occurred at the junction of the veins with the vena cava. In Case II the fibrous plate bridging the orifice of the hepatic vein has been preceded by projecting thrombi of the form seen in Case III. The condition seen in the ostium of the vein which opened into the lower part of the inferior vena cava in Case II probably represents a stage in the formation of the fibrotic disk. Here a sharp projection of intima around the ostium merges into a central thrombus which is undergoing organization. In Case I the thrombosis has extended further down the hepatic veins. The diaphragmatic constriction of the vena cava can also be readily explained on the assumption that a thrombus was primarily deposited at the angle of junction of the stream of the vena cava with the converging streams of the right and left hepatic veins. The fibrous projection of the intima which causes this constriction resembles in form the thrombi which in Case III have been deposited at the junction of the streams in the vena cava and its branches. That the intimal plaque in Case I represents an organized, parietal thrombus can scarcely be doubted. The absence of blood pigment in all the intimal pro-

jections, with the exception of the few granules which were found in the plaque in Case I, does not exclude thrombophlebitis. Thus Case III shows that the thrombus may be almost entirely free from red corpuscles.

The thickening of the intima which is seen in many of the large hepatic veins behind the constrictions is probably a secondary development. Thus in Case II, section 2, it arises in the hepatic vein at some distance from the ostium. In Case I a similar intimal thickening is present in some of the larger canals within the fibrous plug which occludes the lumen. This intimal thickening is of delicate structure and free from vessels. It is not as rich in elastic fibres as the intimal thickening which is commonly met in veins subject to pressure, and which appears to be analogous to the thickening formed in atheroma of the arteries by reduplication of the internal elastic lamina. Intimal thickenings of similar structure may, however, occur in varicose veins.

The thrombophlebitis was doubtless due in part to an infection of the blood-stream, but in neither case is it possible to form even a conjecture as to the nature of the infection.

The macro- and microscopic changes described by Chiari, Lichtenstern, Craven Moore, and Penkert resemble closely those found in the two cases of this paper. Kretz mentions his cases as examples of the condition found by Chiari, but he gives no details. In Chiari's first case the obstruction differed in that bracket-like thickenings of the intima projected from the margins of the orifices, narrowing but not completely occluding the lumen. A similar condition was found in the orifice of one vein in his third case. As stated above, thickenings of the intima of this form probably represent an incomplete development of fibrotic disks such as were present in Case II.

The large right and left hepatic veins at the anterior extremity of the inferior vena cava were obstructed in all cases. Chiari's third case resembles the two cases described here in that the occlusion undoubtedly occurred at the entrance of the branches into these main trunks and not at the orifices of the main trunks in the inferior vena cava. This is the site in which thrombi were deposited in Case III of this paper. It is not improbable that the obstructions had a similar situation in the other cases. When single large right and left hepatic veins are present in the normal liver they are usually very short. Consequently contraction at the orifices of their obliterated tributaries may, as in Cases I and II, convert them into shallow depressions the significance of which can only be recognized by careful comparison with normal livers. In Craven Moore's case the large right and left hepatic veins alone appeared to be affected. In the other cases a variable number of the ostia of the smaller veins in the inferior vena cava were also occluded. The orifices of all the hepatic veins were affected in the case described by Penkert (1902).

In most cases there were irregular thickenings or plaques upon the inner surface of the inferior vena cava. A diaphragmatic constriction of the inferior vena cava is not described in any of the cases which undoubtedly belong to the

group defined by Chiari. In Rosenblatt's case, however, there was such a constriction in the inferior vena cava at its passage through the foramen quadrilaterum. Secondary thrombosis of the portal vein occurred in Chiari's second case.

In these cases described by Chiari, Lichtenstern, Craven Moore, Penkert, and Kretz, in which the ostia have clearly not been involved by an external inflammatory process, different views have been expressed in regard to the pathogenesis. Penkert (1902) considers that the abnormality is a congenital error in development. In all the cases, however, the ductus venosus has been closed. This, as was first pointed out by Gee (9), is an argument against a congenital origin. A stronger argument is found in the histological structure. The coats of the veins at the site of the obstructions were fully developed. They showed no abnormalities apart from the thickening of the intima, and in many cases a slight amount of fibrosis in the media and adventitia. Further, the intimal thickenings were in histological structure unlike foetal remnants. Following Chiari, the majority of observers have ascribed the changes to a pure endophlebitis, caused by irritants circulating within the blood-stream. Chiari considered that the inflammation was syphilitic, but the evidence in favour of this view is very inadequate in his own cases and is not supported by the cases of others. In his first case the diagnosis of syphilis depended upon the discovery of a small white scar on the left labium majus; in his second case there was an aneurysm of the left ventricle resulting from obliteration of the left coronary artery by a vascular connective tissue which he considered to be syphilitic in origin; in his third case the patient had had gonorrhoea. In the cases of Craven Moore, Lichtenstern, and in one case of Kretz there was no evidence of syphilis; in Penkert's case and a second case of Kretz syphilis must be excluded (Kretz, 1902). Kretz pointed out that the peculiar histological picture is not found in disease of the veins of known syphilitic origin. Influenza (Kretz) and whooping-cough (Penkert) may possibly have been causal factors.

Little information in regard to the etiology can be obtained from examination of the sex and age of the patients. In the six cases in which the sex and age are mentioned (*vide supra*) there are three males and three females. One is a male child of twenty-two months; one is a female of fifty-nine; the remainder are between twenty and thirty, the sexes being represented equally. If the two cases of this paper are included, then in four out of eight cases the patients are married women between twenty-five and thirty. Further, in one of these cases (Craven Moore) the woman had given birth to a child three years previously. Before the birth she had enjoyed good health, after the birth she became ill and suffered from sore throats. In another (Chiari, Case 1) the woman had given birth to her second child two months before the onset of symptoms. In view of the not infrequent complication of pregnancy by thrombosis these facts may be of significance.

There are many objections to accepting the view that the intimal changes are the expression of a pure endophlebitis. The histological structure is unlike

a pure endophlebitis. The very sharply defined focal distribution which is characteristic of many of the lesions is not found in endophlebitis of other veins. Further, there is no satisfactory explanation of the selection of the orifices of the hepatic veins as the site of a limited endophlebitis. Craven Moore (5) suggests that the selection depends upon a local susceptibility. With the cessation of the placental circulation the ductus venosus, which opens into the vicinity of the terminal portion of the right hepatic vein, becomes obliterated; and it is possible that the tendency to obliteration may persist in the immediate environment, to be called into being by some irritant which ordinarily would remain without morbid manifestation. It is, however, very difficult to believe that such a tendency to obliteration should be present in the left vein, and more particularly in the small veins in the rest of the hepatic portion of the vena cava. Kretz (1902) also offers an explanation of the peculiarity of structure and site. He considers that the ostia of the veins are selected because they attach the liver to the inferior vena cava and are therefore exposed to mechanical injury. The peculiar thickening of the intima is a luxuriant scarring of small injuries, which follows the combination of mechanical injury and diminished coagulability of the hepatic blood, if a productive healing of the defects is occasioned by inflammatory excitants within the blood-stream.

The view put forward in this paper that the obstructions are due to a thrombophlebitis obtains no support from these authors. Lichtenstern (13) dismisses this view on the ground that in his case no pigment was found in the tissue within the veins. But a little pigment was present in Chiari's first case and in Craven Moore's case. Further, Schüppel (20) describes a case in which there can be little doubt that the obliteration of several large hepatic veins, the superior longitudinal sinus, and both lateral sinuses was the result of thrombosis. In this case the tissue within the hepatic veins was almost devoid of pigment. The almost complete absence of red blood corpuscles from the recent thrombus in Case III of this paper shows that little or no pigment would be present in the fully organized clot.

The points which cause difficulty in the acceptance of the pathogenesis of a pure endophlebitis in these cases are, as has been shown above, actually in favour of thrombophlebitis. The obstructions resemble in histological structure organized tissue. The sharp demarcation of the structures has its counterpart in deposits of thrombus; the peculiar bracket-like form which is met in some cases has been shown to be identical with that in which thrombus may be deposited at the orifices of the hepatic veins. The orifice of the veins is the site which on *a priori* grounds would appear to be the site of election for thrombosis, and the third case in this paper demonstrates that localized thrombi are deposited in this position. The obstructions to the smaller veins are situated in the orifices in the inferior vena cava; in the large right and left veins they lie, at any rate in some cases, in the orifices of the tributaries. These are the identical sites in which thrombi were deposited in the third case of this paper.

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DESCRIPTION OF FIGURES.

PLATE 15. FIG. 1. From Case I, Section 1. Microphotograph of longitudinal section through an obliterated vein which entered the concavity representing the left main hepatic vein. The terminal extremity of the vein lies at the upper end of the figure.

FIG. 2. From Case II, Section 1. Microphotograph of longitudinal section through a tributary entering the left main hepatic vein. The cribriform disk of fibrous tissue crosses the ostium of the tributary.

FIG. 3. From Case II, Section 2. Microphotograph of longitudinal section through the orifice of a small hepatic vein opening into the lower part of the vena cava.

FIG. 4. From Case III. Microphotograph of longitudinal section of anterior wall of an hepatic vein opening into the inferior vena cava. The cava lies at the upper end of the figure. The thrombus rests upon the angle of junction between the hepatic vein and the inferior vena cava.
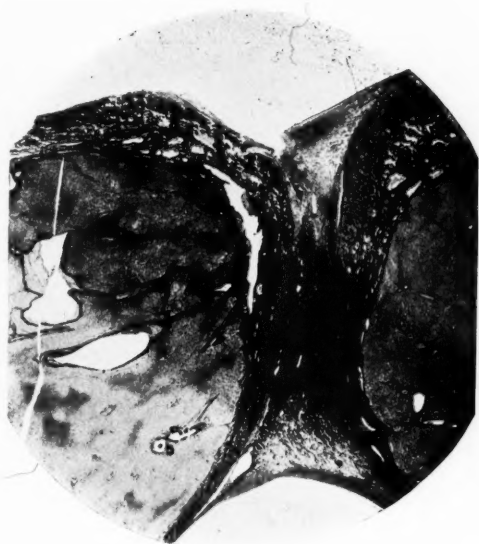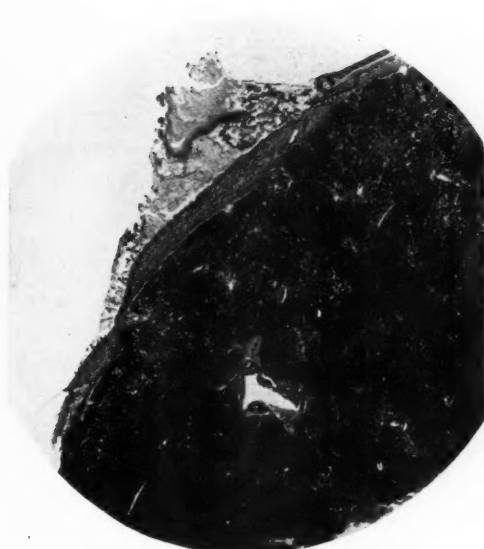
FIG. 1

FIG. 2

FIG. 3

FIG. 4

CRITICAL REVIEW

THE DIGITALIS PREPARATIONS EMPLOYED IN MEDICINE

By W. E. DIXON

SINCE the introduction of digitalis as a remedy by Withering in 1775, few drugs have received more consideration from both chemists and pharmacologists, and a constant stream of literature dealing with both its action and chemistry still continues. Its value as a remedy in disease having long since been established, much attention has been directed in recent times to the best form in which to administer it. The practical importance of this subject depends upon the fact, now well recognized, that the amount and character of the active constituents vary according to the season, soil, and parts of the plant used. The seeds, for example, are not infrequently used in the extraction of the active principles, because they give a considerably larger yield of glucoside for the preparation of the various substances of commerce; but the seeds in contrast to the leaves contain very little digitoxin, which is generally considered the most valuable constituent as regards therapeutic properties, and a relatively large percentage of digitonin which has little or no use as a cardiac tonic. Fränkel showed in Germany that tinctures of digitalis varied as regards cardiac efficiency from 100 per cent. to 400 per cent.: Houghton and others showed the same broad facts in America and Haynes in England. Focke (5) has drawn particular attention to deterioration with age, to the fluctuating amounts of the active principle, and to the fact that the cultivated leaves only contain half the glucoside content of the leaves of the wild plant.

The physician requires then as a first essential an active principle or Galenical preparation of definite and constant composition which represents the full therapeutic activity of powdered digitalis leaves, and the search for the desired substance would naturally lead first to an examination of the chemistry of the plant. The state of our chemical knowledge of digitalis is, however, in a condition of complete confusion. This has arisen largely because the various investigators have described impure substances obtained by dissimilar methods from different parts of the plant, and the difficulty has been increased by the relative insolubility in water of the constituents: the inevitable has resulted and the same glucoside has been described under several different names.

Homolle and Quenne (13) in 1844 were first in the field to give an account of the composition of digitalis : they isolated an amorphous product which they termed digitalin : its physiological characteristics were variable and clearly indicated that it was a mixture of substances. Nativelle (22) separated by means of chloroform a crystalline body of constant composition and action, to which he also gave the name digitaline. Schmiedeberg (26) and later Arnaud (1) gave an account of two new constituents. Killiani in a series of papers has described clearly the exact methods of isolation of the glucosides and their chemical and physiological properties. Houdas also has given an excellent account of the various glucosides.

The same glucoside has been frequently described under several different names : thus Schmiedeberg, adopting a method of extraction different from that of Nativelle, prepared his digitoxin, which was a purified Nativelle's digitaline. Schmiedeberg also isolated a saponin in an amorphous state which he called digitonin ; Houdas crystallized this substance and called it digitaleïne, using a word which had already been given by Schmiedeberg to an entirely different substance.

To follow these controversies would serve no useful purpose, and in the table below the composition and synonyms for the various digitalis principles are given so far as our present knowledge allows for certain.

Glucosides of Digitalis folia, with their synonyms.

Digitoxin. Insoluble in water, but soluble in chloroform.	Digitaline crystallisée (Nativelle), not quite pure. Digitaline crys. chlorof. (French codex). Digitaline amorph. (Homolle), variable in composition and contains a little digitalin.
Digitalin. Insoluble in water and only slightly soluble in chloroform.	Digitalium pulv. pur. Germ. (A mixture of digitonin and digitalin. Soluble in water.) Digitaleïne (Nativelle). Digitalinum verum (Killiani). Digitaline amorph. (French codex).
Digitonin. Soluble in water.	Digitaleïne (Houdas). Digitalinum verum (German Pharm.).

But besides these three glucosides, of which we can speak with tolerable certainty, many others have been described without any real evidence to show that they are distinct chemical substances : such are :—

Digitaleïn. Soluble in water, insoluble in chloroform.	Digitoxin (Keller). Gitalin (Kraft) ? Digalen (Cloetta) ? Digitalinum pulv. pur. German.

Digitophyllin.

Schmiedeberg's digitaléine is a white amorphous powder soluble in water, and digitophyllin is a crystalline body extracted from the leaves, but there can be little doubt that they are only slight modifications or mixtures of the three principal glucosides and consist mainly of digitalin.

The properties of these three glucosides may be briefly described.

Digitonin is a saponin found principally in digitalis seeds, which has no value as a cardiac tonic; its presence with that of other saponins in digitalis leaves is of great importance, since it is owing to this that the pharmacologically active glucosides, digitoxin and digitalin, find their way into the watery preparations such as the infusion. Digitonin was first prepared by Nativelle, but Killiani and Schmiedeberg obtained it pure, the former by repeated crystallization from alcohol. It is soluble only with difficulty in cold water, but is much more soluble when mixed with digitalin, the solubility of which is also increased. Most of the so-called soluble digitalis glucosides are probably formed in this manner. Digitonin combines with many alcohols and phenols forming crystalline substances. It has all the characteristics of the saponins, being irritant and causing the well-known haemolysis; but the latter action is of little significance when the drug is taken by the mouth, since it is not absorbed. The saponins do not bring all the glucosides into solution, since Focke found that about 20 per cent. of the active constituents of digitalis leaves were not represented in the infusion, and recommended the addition of 5 per cent. of alcohol to increase and enhance the value of this preparation.

Digitalin is one of the two active constituents of digitalis leaves; it has an effect on the heart similar in the main to that of digitoxin, but is only about half as active. Although in the pure state it is insoluble in water, it is so easily rendered soluble, as for example by a little digitonin, that it is employed almost exclusively in the preparation of 'digitalin' tabloids and solutions for hypodermic injections. Pure digitalin is not a commercial product, so that if this name is entered on a prescription without further details the choice of a product is left to the dispenser, who will probably employ the digitalinum pulverisation purum Germanicum, a mixture of digitonin and digitalin, and though each of these glucosides separately is soluble with difficulty in water, together they are easily soluble. Digitalin, like digitoxin, constricts the splanchnic vessels though in a smaller degree, but unlike digitoxin the peripheral vessels dilate. It is generally said to be non-cumulative, but this is certainly not correct, and plenty of evidence exists to prove that if it is given in a sufficiently large dose cumulative effects can be obtained; nevertheless, it does not tend to accumulate to the same degree as digitoxin. Digitalin injected under the skin causes pain and inflammation, though this is distinctly less than that caused by digitoxin. In England the doses of most of these digitalis glucosides given to patients are much smaller than those given abroad. In acute cardiac cases $\frac{1}{2}$ gr. in solution may be administered every four hours for two or three days without causing cumulation, and $\frac{1}{4}$ gr. doses may be continued for weeks without harm. To administer doses of $\frac{1}{20}$ gr. is useless for any emergency in which a rapid action is desired.

Digitoxin is not a true glucoside like digitalin, but is probably a pentoside and is the most active constituent of digitalis leaves. Good leaves should contain on an average about 0·3 per cent. digitoxin, but the percentage varies according to the season, being greatest if the leaves are picked in August or September, after which months the quantity rapidly diminishes.

Digitoxin is easily destroyed by enzymes, and it is not unlikely that such an effect may occur at times in the intestines and lead to a diminution in its action. Although the physician requires without doubt the effect of digitoxin on his patients, and although it may be taken as a general axiom that when absorption of a drug is desirable, that event is best obtained by giving the active principle rather than a Galenical preparation, yet the pure substance is in this case not satisfactory. Its insolubility renders it difficult to deal with; it is very irritant, and given by the mouth causes gastric symptoms more frequently than any other digitalis preparation; and if it be administered under the skin, besides the severe pain, it may induce necrosis and suppuration. The other objections to digitoxin are common to most other preparations of digitalis—its slow absorption, its slower elimination, and therefore its tendency to cumulation. Schmiedeberg (27) states that the different constituents of digitalis are absorbed at different rates and that gastric irritation delays absorption. Digitoxin differs from digitalin in that it constricts all vessels and in a more marked degree than digitalin, so that digitoxin raises blood-pressure quite decidedly and largely by vaso-constriction. The coronary vessels are constricted by digitoxin along with the other vessels, this being probably one of the objectionable effects of digitoxin and one not likely to improve the nutrition of a diseased heart.

Huchard (16) has recommended the general employment of digitoxin (crystalline digitalin) as a substitute for the Galenical preparations; he states that he can get a cardiac tonic action in thirty minutes and a diuretic effect in twenty-four hours or longer. He adopts one of the following three methods:—

1. Massive doses are used in severe oedema and anuria. Fifty minims of a 0·1 per cent. solution are given once or perhaps twice in one day and the dose repeated in eight or ten days if necessary. Free diuresis occurs in thirty-six or forty-eight hours.

2. Moderate doses are used in dyspnoea and mitral stenosis. Five to ten minims are given daily for five days and then omitted for three or four weeks.

3. Small doses are used in chronic conditions. Two or four minims are administered daily for weeks or months.

The use of digitoxin by hypodermic injection has been recommended by Marignac and Rosenthal, who have prepared a 'digitalinic oil' in which the digitoxin is in solution. Huchard, who uses this when a very rapid action is desired, states that it produces a constant cardiac effect, and that he has never seen it induce irritation or inflammation.

Methods of administration.

One object in preparing substitutes for the Galenical preparations of digitalis has been that a form might be discovered suitable for injection. Although oral administration suffices for all ordinary purposes it possesses certain drawbacks. Objectionable gastric symptoms are more likely to occur, it takes at least two days to produce an effect on the heart and kidneys, and when the alimentary canal is in a state of bad nutrition, as it may well be in cases of cardiac failure, absorption is apt to be delayed. The direct effect of the drug on the stomach has been avoided by administration per rectum, and some physicians have recorded satisfactory results by using this method.

No active preparation of digitalis is yet known which can be injected under the skin without causing more or less pain and inflammation, and the most irritant of all such preparations is crystalline digitoxin. Moreover, the intramuscular injection of digitoxin, digitalin, and their preparations is not unattended by pain, so that for routine use neither of these methods of administering digitalis is appropriate. But the evidence suggests that in a suitable form this drug may usefully be injected intravenously without any evil secondary effect. Most drugs injected intravenously are rapidly excreted from the blood, so that the specific effect lasts only a few minutes. With digitalis this is not the case: the glucosides are stored in the tissues, especially the heart, and an intravenous injection of digitalis does not cause its maximum effect on the heart for perhaps two or three hours later, and the effect lasts several hours. It is true that an increase in blood-pressure may be observed in a few minutes, but this is vaso-motor in origin and need not be associated with a more 'efficient' heart-beat. There can be little doubt, however, that if a form suitable for intravenous injections can be obtained, this method of treatment would be largely extended. The injection of infusion of digitalis is said to be attended by febrile symptoms due, according to Focke, to the 'albuminoids'. Dialysed solutions from which these albuminoids had been excluded, according to Mendel, induced giddiness and oppression. Digalen exerts, according to Hale, some stimulant action on the central nervous system in animals, and Teichmann (32) has recorded a similar effect in a patient after taking 4 c.c.; oedema and thrombosis are also recorded as following intravenous injections of digalen. Digitalone is recommended strongly by Mendel as a drug suitable for this method of administration: but reliable clinical reports are too few to draw any certain conclusions. Clinical data on digipuratum are also not sufficiently numerous to warrant any definite report being made as to its value as an intravenous injection. But neither of these two preparations is said to produce any very serious after-effects, and both deserve an extended trial.

It is clear that the digitalis glucosides and Galenical preparations possess certain objectionable properties; they derange appetite and digestion, they are too irritant for injection purposes and tend to cumulate in the system. All these facts render it necessary that the drug should be administered, in anything but

the smallest doses, with considerable caution.   Another objection to their use is
the fact that the therapeutic effects, especially the diuresis, do not appear before
the second day, and more commonly on the third, and this renders the drug of
little value in acute conditions, and when an immediate action is required.
Various attempts have been made to provide a digitalis derivative possessing all
the virtues of digitoxin without these objectionable effects; the three most
important proprietary preparations which have been introduced with this object,
digalen, digipuratum, and digitalone, must receive further consideration.

Digalen or ' digitoxin solubile' is an amorphous powder which bears certain
chemical and physiological resemblances to digitoxin.   It is not, however,
the same substance as the crystalline product of Schmiedeberg and Killiani,
since it is amorphous, soluble in water, considerably less toxic, and has
a slightly different action.   It is placed upon the market as an aqueous solution
containing 25 per cent. of glycerin.   One c.c. of this solution corresponds with
0·15 gramme digitalis folia, so that an average dose would be about 15 minims
or 1 c.c., and this would correspond with 0·3 mgr. digalen.   Killiani (17), who
is perhaps the greatest authority on the chemistry of digitalis, believes that it is
mainly ' digitalëin ', and its toxicity certainly corresponds more closely with this
substance than with digitoxin.   It was prepared first by Cloetta (2), who claimed
for it a superiority over digitoxin, in that it was soluble in water, less irritant,
and so less likely to give rise to disorder of the stomach, more constant, being
regarded by him as a definite chemical compound, more rapid in its action,
in which case it should be of special value in acute infectious diseases, and lastly
that it was not cumulative like digitoxin.

Cloetta admits that digalen is less toxic than digitoxin, whilst being just as
efficient therapeutically : in other words, he believes that its therapeutic dose
is much further removed from the toxic dose than in the case of digitoxin.
Digitoxin causes death by its direct action on cardiac muscle, and the principal
therapeutic . effect is caused in the same way and is generally regarded as a
different degree of the same effect, so that its toxic action is an excess of the
therapeutic effect.   It is difficult then to understand the position of Cloetta, who,
whilst claiming that he is dealing with a digitoxin equal in therapeutic efficiency
with Schmiedeberg's digitoxin, yet claims that it does not lead to poisonous
symptoms.   Experiments which are now being made in Cambridge do not
uphold this view ; they rather go to show that both the toxicity and therapeutic
efficiency are some two or three times less than digitoxin.   That the toxicity,
however, is much less has been clearly shown by Neave (23), Hale (10), Symes (30),
and Hatcher (11) ; the last observer found digalen about a quarter the strength
of crystalline digitoxin.   Kottman, however, and others from clinical observations
have stated that it equals crystalline digitoxin in therapeutic activity.   Haphazard
clinical observations on the value of digitalis bodies are valueless and worse, on
account of the extreme difficulty of measuring the heart's activity.

Worth Hale showed that digalen varied in value to 100 per cent., probably
as a result of deterioration with age.   It was much inferior in toxicity to

digitoxin, about one quarter, and more nearly approached digitalëin, but was a little more toxic than that substance.   According to Hale also, digalen acts more as a stimulant to the central nervous system than either digitoxin or digitalëin.   In mice a distinct tendency to convulsions occurs, and Teichmann has seen similar symptoms from the intravenous injection in man.

Clinicians vary in the widest degree in reports as to its clinical value ; some think that it is an ideal digitalis preparation, whilst others regard it as unsatisfactory, and state that it is apt to cause secondary objectionable effects.

Digalen is said not to be so irritant to the stomach and alimentary canal as digitoxin, and this is probably true ; nevertheless, it is not without irritant properties, and Eichorst (3), Veiel (34), Teichmann (32), and Müller (20) regard its untoward effects on the alimentary canal as of the same order as the Galenical preparations.   The probability is that its alimentary effects, such as loss of appetite, nausea, and vomiting, which are caused by the specific action of the glucosides on the muscle of the stomach, bear a definite relation to its action on cardiac muscle, and as this appears to be less than that of crystalline digitoxin its alimentary effects will no doubt be less in the same proportion.

The claim, at first made, that it was less irritant than other digitalis preparations when injected under the skin cannot be accepted ; digalen is an extremely irritant substance to employ hypodermically, and pain, swelling, and inflammation are the usual sequence of such an injection, just as in the case of digitoxin.   This led to the deep intramuscular method of injections much in vogue in Germany : thus Eulenberg (4) injects 1 c.c. into the gluteal muscles, and this dose he repeats when necessary ; but even such injections, as Stadelmann (29) has pointed out, produce considerable pain and inflammation, generally of a temporary character, it is true, but quite sufficient to cause patients to object to further treatment.   Teichmann (32), Kottmann (18), Hochheim (12), Veiel (34), and others are agreed that it is inadvisable to employ subcutaneous injections of digalen on account of these marked irritant properties.   Even by intravenous injection the drug is not free from danger, since thrombosis and oedema have been reported as sequels to such administration.

Digalen is said to be more rapid in its action when taken by the mouth than the Galenical preparations ; if this is so it is a matter of some importance, as in some acute diseases a rapid action is often most desirable.   Kottmann says that 0·3 mg. digalen injected subcutaneously produces a distinct digitalis action twenty-four hours later : he also says that intravenous injections cause a rise of blood-pressure in from two to five minutes which lasts twenty-four hours.   It is, of course, the easiest thing possible to induce a rise of blood-pressure by an intravenous injection of various drugs.   Barium salts will do this to perfection, but the effect is vaso-motor : the object of employing digitalis is to increase the cardiac efficiency, not the peripheral resistance, and of this Kottmann gives no evidence, and as in his patients the pulse rate was practically unaltered the rise of blood-pressure was no doubt due to vaso-constriction.

v. Naunyn obtained a digitalis action twenty-four hours after digalen had been

given by the mouth, and he says that it acts quicker than inf. digitalis : also Freund (7) regards digalen as a most satisfactory preparation of digitalis. The results of Müller, Fränkel (6), Gröber (9), Walti (36), and Teichmann (32) show clearly, more especially those of Müller, that digalen is no more rapidly absorbed than powdered digitalis leaves as measured by the action on the rate of the heart-beat and on diuresis.

Lastly, it is claimed that digalen is not so *cumulative* as digitalis folia or digitoxin. Cumulation is the result of an excess of absorption over excretion. A single dose of digitalis does not produce its maximum effect for some two days, and the action may be prolonged as long as ten days ; how it is stored up in the body is not known with certainty, but one place is probably the heart-muscle. If a single dose of digitalis be given to an isolated and actively beating mammalian heart perfused with blood or Ringer's solution, so that the drug passes through the coronary vessels for a very short period—let us say one minute— and is then immediately replaced by normal perfusing fluid free from digitalis, in this short time sufficient may be absorbed into the heart-muscle to cause death. The heart may be quite uninfluenced for half an hour or an hour ; the digitalis action then progressively increases and may cause death in tonus some three or four hours later, clearly showing that the drug is stored up in some fashion at present unknown.

Cumulation may result from a number of small doses of digitalis, and give rise to symptoms which are indistinguishable from a single large one ; these symptoms are dryness of the throat, a bitter taste, vomiting, diarrhoea, and later arrhythmia, tachycardia, and intense vaso-constriction. Fränkel has shown that a daily fixed maximum dose can be tolerated for weeks without ill effects, but that if this be exceeded at any time by ever so little, toxic symptoms supervene.

Cloetta's experiments to show that digalen was not cumulative were verified by Freund (7) and Sasaki (25) ; Cloetta later modified his first view and states that both digitalis folia and digalen can accumulate in the system, but cumulation is not so regular as with digitoxin, and he regards the deciding factor in cumulation to be the crystalline nature of the digitoxin. Gröber (9) is sceptical as to any difference of cumulative action between digitoxin and digalen, and Westenrijk (37) finds no important difference in action between digitalis and digalen, and thinks they have the same cumulative effect. Fränkel (6) says cumulation can be obtained with digalen, and from a number of experiments concludes that the experiments of Cloetta and others, who failed at first to obtain cumulation with digalen, were due to the fact that they used either too small doses or their experiments were not continued for a sufficiently long time. Vlach (35), Müller (20), and Reitter (24) also show that cumulation may result, and Umber (33) regards digalen as equally cumulative with digitoxin.

It may be concluded then that conclusive evidence, either pharmacological or clinical, is lacking which would place digalen in a position superior to the Galenical preparations of digitalis. It is not more rapid or constant in its

action than a properly standardized tincture; it is irritant, causes gastric symptoms, is cumulative, and is not a suitable preparation for injection.

Digipuratum is a preparation made from digitalis leaves by exhausting them with alcohol and ether. By this means Gottlieb (8) states that 85 per cent. of the inert material in digitalis leaves including the saponins is removed, and that the remaining 15 per cent. contains all the active constituents with the exception of about 5 per cent. On drying *in vacuo* a powder is left, the action of which, as well as its digitoxin content, is said to remain constant for years. Digipuratum is insoluble in cold water and dilute acids, but is soluble in 0·1 per cent. sodium bicarbonate, and consists of a mixture of the tannic acid compounds of the glucosides; it is standardized to contain a fixed amount of digitoxin. Hale (10) examined different examples bought in the ordinary retail fashion, and states that it is of the same strength whether bought in tablet or powdered form.

Digipuratum has about half the toxicity of ordinary digitalis leaves (Schüttler (28)), and is certainly much less toxic to dogs than a corresponding quantity of the leaves (Frohner). It has one advantage over the tincture of digitalis, in that it exerts no direct action on the stomach, since the irritant substances other than the useful glucosides have been removed, and the glucosides cannot be irritant since they are not soluble in the acid gastric juice. This is further shown by the fact that if animals are poisoned with digipuratum the mucous membrane of the stomach appears normal after death, whilst the intestines and kidneys exhibit catarrhal changes (Franzen). The four virtues which can be assigned to digipuratum are that it keeps well, it is uniform in composition, it contains all the glucosides of value in digitalis, and causes less gastric irritation than the powdered leaves.

Clinical reports on the value of digipuratum are on the whole favourable. It has been used in the Massachusetts General Hospital in the treatment of more than 180 patients, and the report says that it is prompt in action and that vomiting, diarrhoea, and cumulation were absent (38). In treating severe cardiac failure four tablets were given the first day (0·1 grm. each), three the second, three the third, and two the fourth, that is 1·2 grm. in four days, but in very severe cases the drug was continued for a longer period.

Höpffner (14) also found it reliable, prompt, and less likely to disturb the stomach than other preparations of digitalis. Gröber says that it has the same cumulative action as digitalis, but thinks he obtained better results with this body than with a single isolated active glucoside. Müller (21) says the effect was apparent on patients after 0·4 grm. on the second day, and after 0·3 grm. on the third day, and agrees that gastric symptoms are rare. Gastric symptoms such as loss of appetite, nausea, and vomiting may however occur, as shown by Szinnyei (31).

It is well to remember that gastric symptoms may arise in one of two ways: they may be due to the direct irritant action on the stomach, brought about by digitonin ferments, pectin, or soluble glucosides, or they may be caused after

absorption by the direct action of the digitoxin on plain muscle; gastric symptoms caused by the administration of digipuratum must be due to the specific action of the drug on the gastric muscle after absorption.

Digipuratum is said to contain all the active glucosides of digitalis in an unmodified form and in the same proportion in which they occur in the leaf. If it is essentially of the same constitution, its therapeutic dose should bear the same relationship to its toxicity as in the case of digitalis, which is said not to be the case.

We may sum up then by saying that digipuratum is a uniform and reliable preparation of digitalis, it keeps well and contains all the cardiac glucosides; but all this is true of a properly standardized tincture of digitalis, for, as Haynes has shown, such a tincture will keep for two years without undergoing any material alteration in activity.[1] It has one advantage over tincture of digitalis in the absence of inert matter, some of which may directly irritate the stomach, but it is doubtful whether this relatively insignificant advantage can make up for its being some ten times more expensive.

Digitalone is another preparation said to contain all the active constituents of the leaves; 10 minims of the solution correspond with 1 gr. of leaves. The solution is alcohol-free and contains 0·6 per cent. chloretone as an antiseptic; like digipuratum it is standardized by physiological methods.

Digitalone, like digalen and digipuratum, has a typical digitalis action on the heart, and it is claimed for this preparation by the manufacturers that it is suitable for oral hypodermic intravenous or rectal administration. So far as my own knowledge of the action of this substance goes it exhibits no important qualitative differences from the ordinary Galenical preparations, but it is less active; it appears to be absorbed at about the same rate and to accumulate in the same way.

Houghton (15), from experiments on animals, concludes that in the form of subcutaneous injections it is much less irritant than either digitoxin, digitalin, or a fluid extract of the leaves. In man, although the same fact is probably quite true, it is also certain that subcutaneous injections of digitalone cause so much pain and swelling as to render this method of administration unsuitable. Mendel (19) speaks highly of the value of digitalone for intravenous injection, especially in patients when the customary methods of administration are attended by ' dangerous or unpleasant consequences ', when there is reason to believe that the drug is not absorbed, or when an immediate effect is desirable. He employed it in seventy patients suffering from various kinds of cardiac disease, and recommends a dose of 2 c.c. (0·2 grm. digitalis folia). From such a dose he says evil effects do not occur. Other clinicians, however, such as Gröber (9), state that in their hands it has not been satisfactory.

In conclusion it may be stated that pharmacological and clinical investigations

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[1] This does not agree with the observations of Hales and others in America, who found that digitalis preparations depreciated with age even in two years. Haynes kept his preparations in the dark.

have not made a clear case for the substitution of 'active principles' for Galenical preparations of digitalis in the treatment of patients. These active principles are for the most part just as irritant as the infusion or tincture; they are neither more reliable and constant in action than a properly standardized tincture, nor are they absorbed more rapidly; they have the same tendency to accumulate and are much more expensive. The one advantage that certain of them may possess over the pharmacopoeial preparations is that they may be given intravenously without ill effects.

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THE ASSOCIATION BETWEEN MITRAL STENOSIS AND RENAL FIBROSIS

By JOHN COWAN AND GEOFFRY B. FLEMING

MITRAL stenosis has well been called the land of romance, for there is probably no cardiac lesion which has produced so copious a literature or around which have centred so many controversies. And even now, although it is nearly seventy years since Fauvel first recognized the characteristic crescendo murmur, there are many points that are still unsettled. The characters of the pulse in this disease, the cause and even the rhythm of the murmur, the reason of its special frequency in the female sex, its relationship with pulmonary phthisis, and its etiology, are still disputed.

It seems strange that the characters of the pulse in mitral stenosis should still be discussed, but a very short survey of the literature shows a notable difference of opinion. George Balfour (1), for example, stated that the pulse was weakened in exact proportion to the degree of the stenosis, and that it was more or less irregular, a fact of diagnostic significance; while William Broadbent (3) maintained that it was a small pulse, full between the beats and not very easily compressed, and that it was almost always regular unless the heart was obviously failing; he considered that it was in mitral incompetence that the pulse was irregular.

The second part of the controversy has been decided by recent research. Clinically , as Graham Steell (26) has shown, 'the murmur most frequently present in cases of mitral stenosis is unquestionably the murmur of coincident mitral incompetence . . . (which) is usually the only mitral murmur present up to the end'; and it is now known (Rothberger and Winterberg (22), Lewis (16), Ritchie (15)) that the pulsus irregularis perpetuus is usually due to auricular fibrillation, an incoordinate fluttering of the auricular fibres replacing the normal co-ordinate auricular contraction; and that with the onset of fibrillation the characteristic crescendo murmur disappears. So that both authors are correct in their statements. An irregular pulse is most frequently associated with the murmur of regurgitation, but post mortem with a stenosed orifice.

The contradictory statements with regard to the blood pressure have received as yet but scant attention, and G. A. Gibson (9) seems to be the only authority who has attacked the problem with the aid of the sphygmomanometer. He states that the blood pressure in mitral stenosis is ' often below the

normal, but even more frequently above it '. Our own results agree with this statement.

Fig. 1 shows the maximum systolic pressures recorded during their stay in hospital in fifty-nine cases of organic mitral disease. We have not separated the cases with stenosis from those with regurgitation on account of the difficulty of accurate diagnosis, and because the cases are in no way comparable, for some of the patients were *in extremis*, others were convalescent; some were notably oedematous, others were not; some had many complications, others were pure examples, &c. But it is evident that the pressure varies considerably in different cases, the extremes being 95 and 215 mm. Hg.; and in thirty-six of the fifty-nine the pressure is above the average for the particular age as shown in Woley's (28) tables. In mitral disease an elevated blood pressure is not the result of the cardiac lesion. Mitral disease is not comparable to aortic regurgitation, for example, where the 'pulse pressure' is an index to the degree of the valvular flaw. In aortic regurgitation, the regurgitation of blood into the ventricle during diastole necessitates an abnormally large systolic output, if the aortic content during diastole is to remain normal; and similarly, the rapid fall of pressure during diastole requires an abnormally high initial pressure if the mean aortic pressure is to remain normal. In mitral disease the difficulty lies in securing a sufficient supply of blood for the aorta, and an elevated blood pressure can only be due to causes acting outside the heart.

In mitral stenosis the left ventricle is often, as one would expect, of normal size and contrasts with the enlarged right heart, but it is not infrequently hypertrophied. Sansom (24), for example, found it hypertrophied in nine, and small or of normal size in fifteen, out of forty cases examined post mortem. In cases with coincident mitral reflux or aortic valvular disease, the hypertrophy is, of course, the result of the additional lesion, but in the pure cases the cause must be sought for outside the heart, and the explanation is evident when it is recognized that a high blood pressure not infrequently obtains, for the latter, if continuous, will very soon produce hypertrophy.

The causes of an elevated blood pressure are numerous and well known, but need not be referred to here in detail. It is sufficient to recall that chronic nephritis of the cirrhotic types and arterial disease are the diseases in which the blood pressure is most commonly elevated to considerable heights, and the left ventricle most frequently hypertrophied.

Our post-mortem experience of uncomplicated mitral disease is at present small and comprises only fifteen cases, but in ten of these the kidneys were found to be more or less fibroid (capsules adherent; surface more or less granular).

Fig. 2 shows the blood-pressure readings in eleven of these fatal cases; in eight it is above normal, and in three below normal. Two of the cases with abnormally low pressure had kidneys which were fibroid, and the recorded pressures must be regarded as evidence of extreme cardiac failure at the time when the observations were made. Two of the cases with abnormally high pressure had kidneys

which were not fibroid. In one, a boy of 13, oedema was notable and albuminuria considerable; in the other, a woman aged 35, there was oedema and effusions into the sacs, and the urine habitually contained blood and albumin
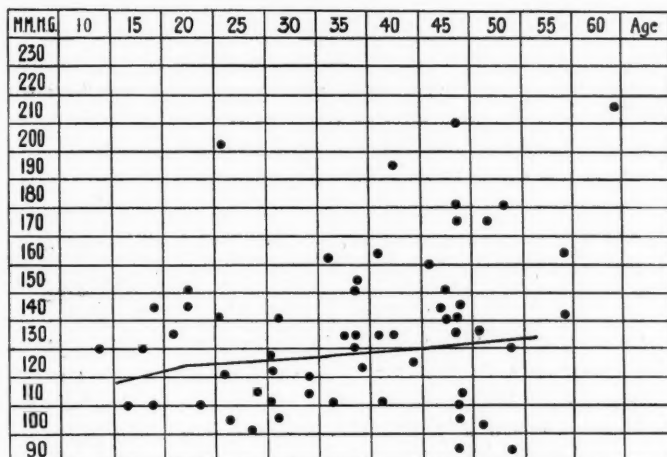
MAXIMUM SYSTOLIC PRESSURE
Mitral Disease, All Cases.

FIG. 1. The black line indicates the average normal systolic pressure (Woley).
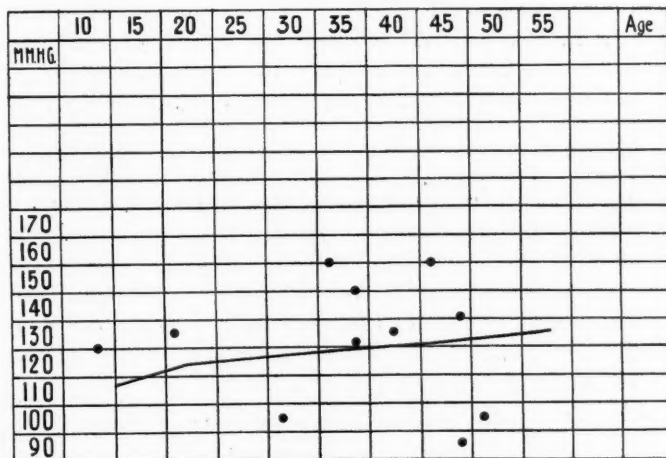
MAXIMUM SYSTOLIC PRESSURE
Mitral Stenosis P. Ms.
FIG. 2.

in large amount. So that in both cases other causes of a high blood pressure were active at the time of the observations.

It has been known for long that there is a close connexion between mitral and renal disease. Barclay (2) was the first to point this out. Examining

post-mortem data, Goodhart (12) found that of 97 cases of renal cirrhosis 47 had mitral lesions in addition, while of 215 cases of (clinically) primary cardiac disease 31 had cirrhotic kidneys. Some years later Newton Pitt (21) conducted another similar investigation: of 542 cases of renal cirrhosis 33 had mitral stenosis, while 33 per cent. of 115 cases of mitral stenosis had renal cirrhosis in addition. By the kind permission of Dr. Teacher we have investigated the post-mortem records of the Royal Infirmary, Glasgow and find that the figures show a similar coincidence. Of 335 cases of renal fibrosis 60 had organic mitral disease, and of 93 cases of mitral disease 60 had fibroid kidneys.

We can find but little reference in the clinical literature to this connexion between mitral and renal disease, which is referred to by Sansom (24), H. Huchard (14), and G. A. Gibson (9) alone; and all three are mainly concerned in showing that in certain cases (as e.g. in Sansom's well-known instance) the renal lesion is apparently primary and the mitral stenosis its result. A chronic endocarditis of such an origin is, however, by no means of common occurrence, and can hardly explain the frequency of the combination in the statistics which we have given.

The relationship between the two lesions may conceivably arise in various ways. It may be accidental; the renal lesion may be the cause or the result of the mitral disease; or both may own the same origin.

I. The association may be accidental. The figures which we have quoted seem to us sufficient evidence that the association is not simply accidental, for Newton Pitt found that mitral disease is three times more frequently present in cases of granular kidneys than in those whose kidneys are normal, and in our own series the proportion is even greater [fibroid kidneys, 335 cases; mitral disease, 60 (17·9 per cent.). Kidneys not fibroid, 807 cases; mitral disease, 33 (4·0 per cent.)].

II. The renal lesion may be the cause of the mitral disease. There is no doubt that the majority of cases of mitral disease are the result of an antecedent acute endocarditis of rheumatic origin. We have collected a series [1] of 479 cases of organic mitral disease, and in 275 (57·4 per cent.) the patients had suffered from some form of rheumatism or from chorea. Acute rheumatism too, in childhood, is often associated with an arthritis which is trivial and fleeting, and the rheumatic incidence may be slightly greater than the figures indicate. The other infections which are common in this country have but little tendency to produce endocarditis, which, when it does occur, is not infrequently the result of a secondary pyogenic infection. Scarlatina and pneumonia are the diseases

				Mitral Disease.	Rheumatic History.
Dyce Duckworth (8)	.	.	.	264	141
A. E. Sansom (24)	.	.	.	64	32
G. A. Gibson (10)	.	.	.	76	43
Graham Steell (26)	.	.	.	60	47
Personal	.	.	.	15	12
				479	275 = 57·4 %

in which it is most frequent, but McCollom (17) states that it only occurred 13 times in 2,000 cases (0·65 per cent.) of the former, and Musser and Norris (19) report its incidence in the latter as 0·44 per cent. (32,349 cases).

A fair proportion of these cases, too, are of the malignant type and cause the death of the patient, so that the infections as a whole (apart from acute rheumatism) do not seem to play an important part in the causation of the chronic disease.

A priori there seems little reason why the mitral valve should not be affected by the same kind of primary chronic endocarditis which it is well known not infrequently affects the aortic cusps. Plaques of atheroma are by no means uncommon on the anterior mitral cusp, and it not infrequently shows a diffuse thickening and fibrosis about its base in the regions which are but rarely affected by acute endocarditis.

In a small number of cases of mitral stenosis no recognized cause of acute endocarditis can be discovered in the antecedent history, and in another group it seems unlikely, from the history of the case, that such causes, though they had been present, could be associated with the origin of the valvular lesion. Three such cases occurred in our post-mortem series. In one, a woman aged 45, the patient would not admit having had any illness whatever before the onset of that which ultimately proved fatal. The second, a woman aged 43, had had measles and scarlatina in childhood, but subsequently had always been healthy until a few winters before her death, when she became liable to bronchitis, and short of breath on exertion. The third, a man aged 47, had had no previous illness with the exception of an attack of 'gastric' fever at the age of 14. And lastly, there are a small number of cases on record, in whom mitral stenosis has been observed to develop in the absence of all acute disease.

It is generally agreed that the most frequent causes of these chronic cases are arterio-sclerosis and chronic nephritis, and in all our three cases the kidneys were more or less granular and the capsules adherent.

Huchard has outlined the process by which the lesion is produced. The vessels of the valve in arterio-sclerotic cases have been found degenerate (Martin) and their lumen notably diminished; and in another group of cases minute haemorrhages are not uncommonly present in the anterior cusp (Weber and Deguy). As a result, the overlying endothelium is lost and fibrin is deposited upon the uncovered surface; and the constant movements of the part produce a 'callus' which is large and out of proportion to the original lesion. There is no real division of the mitral valve into separate cusps; it is actually a petticoat with a skirt of varying length; and the ultimate result of cicatrization is always stenosis. The process may be confined to the valve, and a diaphragm results, but the involvement of the musculi papillares and the chordae in the fibrosis produces the funnel form.

It thus seems evident that in some cases the renal lesion is the cause of the cardiac one, but it is improbable that this is the common sequence. It is true that the incidence of mitral disease in cases of renal fibrosis is much greater than

in cases where no renal fibrosis obtains, but the incidence is much greater in women than in men :—

	Renal Fibrosis.	Mitral Disease.	Per cent.
Men	201	27	13·4
Women . . .	134	33	24·6

a fact which suggests that the connexion arises in other ways.

III. The renal lesion may be the result of the mitral disease.

The post-mortem evidence makes it fairly evident that renal fibrosis cannot be the cause of mitral stenosis in all the cases where the two lesions co-exist, and the inference is strengthened by examination of the clinical data. In three of our cases the sequence seemed fairly clear. In one, a man aged 21, who had suffered from chorea at the age of 3, the mitral valve was notably hard and deformed, and the kidneys were only slightly affected. In another, a woman aged 48, who had suffered from acute rheumatism at the age of 22, the mitral valve was seriously involved and the interstitial nephritis was 'early'. In the third, a woman aged 35, who had had several attacks of acute rheumatism before the age of 28, the kidneys were still large, though notably granular. In all three cases the symptoms were cardiac.

It has been suggested (W. Jenner) that the renal fibrosis is the result of chronic venous congestion secondary to the mitral disease, but there is no real evidence that chronic venous congestion can produce fibrosis (R. Muir). If it were a cause, too, the liver should suffer as frequently as the kidneys; but this is not the case, for in our series of 93 cases of organic mitral disease, 60 had renal fibrosis, and only 9 a cirrhotic liver. The causes of chronic renal fibrosis are still unknown, but there is considerable evidence in favour of the view that it is due in many instances to a faulty metabolism and consequent irritation of the kidney by abnormal substances which are excreted in the urine. Chronic venous congestion of the digestive organs is extremely likely to derange their proper action, and it is not infrequently accompanied by gastro-intestinal catarrh which will have its own special action.

Brockbank's (4) experience of the incidence of cholelithiasis in cardiac disease has a bearing upon this point. He found that gall-stones were present (post mortem) in 55 cases (10·9 per cent.) out of 504 cases of gross cardiac disease, while they only occurred in 46 cases (5·4 per cent.) out of 843 cases which had no cardiac disease. Mills (18) made a similar investigation at St. George's Hospital and found that gall-stones were present in 15 per cent. of 200 cases of cardiac disease. There is thus very strong evidence that cardiac disease predisposes to catarrhal conditions of the liver as well as of the gastro-intestinal tract.

IV. Mitral stenosis and renal fibrosis may own the same cause.

It is difficult to assess this proposition at its true value, for there is no real proof of its truth; but there is some very suggestive evidence in its favour.

The special frequency with which mitral stenosis occurs in women (males

482; females 808)[2] has not yet received an adequate explanation. Newton Pitt (21) has suggested that pregnancy and parturition are responsible for a considerable number of cases of granular kidney occurring in women. In his series only two patients under the age of 32 had cirrhotic kidneys; of twenty-three women with mitral stenosis only three had suffered from rheumatism; and it was 'most probable that . . . in most of the cases' the valvular lesion was secondary to the renal one. The incidence of granular kidney in cases of mitral stenosis is, too, greater in women than in men, one-third of the women and only one-fifth of the men having the renal affection.

In our series there is but little difference between the sexes. Of 43 male cases of mitral disease 27 (62·7 per cent.) had renal fibrosis; while of 50 female cases 33 (66 per cent.) had renal fibrosis.

Sansom considered that endocarditis and renal disease might both be set up by causes operating during the puerperium, and so initiate the chronic changes; an opinion which is supported by the fact that Lockhart Gillespie's (11) statistics show that the maximum incidence of mitral stenosis in women is between the ages of 20 and 29.

Nettleship (20) has shown that juvenile interstitial nephritis has a special incidence in the female sex. In Dickinson's series, collected from the records of St. George's Hospital, granular kidney was found to be much more common in men than in women (M. 165; F. 85), death occurring most frequently after 40 years of age (before 40, 56; after 40, 186). But in Nettleship's series under the age of 21, the incidence is reversed (M. 28; F. 51), and the figures are still more striking if the cases are confined to those under 13 years (M. 16; F. 35). He showed, too, that the incidence is peculiar to interstitial nephritis, a similar series of cases of parenchymatous nephritis under the age of 13 containing 70 boys and 60 girls. He has found that interstitial keratitis is more common in girls than in boys (M. 225; F. 339. J. Hutchinson, M. 38; F. 64), and suggests that the peculiar incidence of interstitial nephritis in childhood may be due to an excess of girls over boys born syphilitic surviving early infancy. In his series, however, only six cases were proved to have hereditary syphilis.

Rolleston has suggested to us that syphilis may be the common cause of both mitral and renal disease. It is well known that it may produce any variety of acute or chronic nephritis, the form most frequently encountered being chronic nephritis with amyloid degeneration. But granular kidney is not rare,

[2] Mitral Stenosis.								Males.	Females.
Newton Pitt (21)	.	.	.	.	.	.	.	10	23
G. A. Gibson (9) .	.	.	.	.	.	.	.	324	523
W. Broadbent (3)	.	.	.	.	.	.	.	15	38
Hayden (13) .	.	.	.	.	.	.	.	27	54
Dyce Duckworth (8) .	.	.	.	.	.	.	.	17	63
D. M. Samways (23) .	.	.	.	.	.	.	.	89	107
								482	808

and was present in 16 of 220 syphilitic cases (Speiss (25)), and 18 more showed 'sclerosis' of the kidney. In congenital syphilis renal disease is not uncommon, and was present in 10 of 12 post-mortems (Cassel (6)); while Still (27) reports that in 5 of 10 cases occurring in early childhood or in adolescence the renal change was mainly or entirely interstitial.

It is also recognized that syphilis often originates widespread arterial disease, and is indeed, in childhood, its most frequent cause. In many instances the cardiac valves also suffer, the aortic most usually, the mitral only on occasion. But its real importance among the numerous causes of chronic valvular disease may be obscured by the specific character of the initial lesion being obliterated in the course of years, and so missed on post-mortem examination. Acute syphilis at the present day rarely causes death, but we have observed a case where the kidneys and the mitral valve were affected] in addition to the aortic valve.

The patient was a man, aged 48, of athletic habits who had lived freely. At the age of 44 he contracted a chancre which was not accompanied by constitutional symptoms; he received no specific treatment. Two years later he began to notice that he became very short of breath on exertion, and shortly afterwards the dyspnoea became paroxysmal and acute, and sometimes occurred when he was in bed. Symptoms of marked cardiac failure ensued, and he died about two years after the onset of symptoms.

The striking feature at the post-mortem examination was the intensity and the extent of the arterial lesions, the aorta and practically all its main branches being dilated, while their walls were thickened generally and showed many large soft plaques of atheroma. The aortic valve was notably deformed and grossly incompetent; the mitral valve was dilated and its cusps shortened and thickened; and the surface of the kidneys was slightly granular, and their cortex slightly atrophied.

Scarlatina, as we have already mentioned, is occasionally the cause of acute endocarditis and is well recognized to be often accompanied by acute nephritis (acute nephritis, 4 per cent.; albuminuria, 7·9 per cent. 10,983 cases. Foord Caiger (5)). In the cases with definite symptoms of nephritis, the kidneys show a glomerular nephritis, but an acute interstitial nephritis may be found post mortem in cases which clinically had showed no real evidence of renal affection (Chapman (7)), and may thus initiate the cirrhotic process.

Nettleship investigated the antecedent history of forty-five of his cases of juvenile interstitial nephritis and found that scarlatina was antecedent in sixteen instances (M. 3; F. 13). He points out that according to Dickinson acute nephritis is more common in boys than in girls (M. 58; F. 47), and that death from scarlatinal dropsy is also more common in boys (M. 946; F. 629), although deaths from scarlatina are nearly the same for both sexes. He suggests, therefore, that there may be some difference in the character of scarlatina as it affects the two sexes.

The facts which we have collected are of course no positive proof of the truth

of proposition IV, but they are extremely suggestive. Renal cirrhosis in women causes death at an earlier age than is the case in men (W. P. Herringham), and presumably owns other causes. Renal cirrhosis in childhood occurs more frequently in girls than in boys. Mitral stenosis affects women most frequently in adolescence and early adult life. The puerperal state, scarlatina, and syphilis are known sometimes to affect both the heart and the kidneys, and may conceivably, in certain cases, involve both at the same time.

There is, we think, little doubt that the frequent association of mitral stenosis and renal fibrosis is not accidental, but the relationship between the two is not invariably the same.

In conclusion we may state: the blood pressure in mitral stenosis is often normal or subnormal, but even more often above the average. The persistence of high blood pressure, in the absence of oedema, strongly suggests the presence of renal fibrosis.

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TRIPLE RHYTHM OF THE HEART DUE TO VENTRICULAR EXTRA-SYSTOLES

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OF recent years much light has been thrown on the nature of cardiac irregularities, but we are still largely ignorant of the causes which produce them. And while in many cases of cardiac arrhythmia more than one cause may be active, it seems reasonable to assume that when a regularly recurring irregularity manifests itself, the allorhythmia is dependent on a single cause.

Two cases have recently come under my observation which showed a form of allorhythmia characterized by arrangement of the heart-beats into groups of three, each group being separated from its neighbour by an abnormally long pause. This form of allorhythmia, which may be called triple rhythm, may occur in various forms of irregular heart action. It may be present in the youthful type of irregularity as shown in Fig. 1. Heart-block, where every fourth auricular contraction fails to produce a response from the ventricle, may give rise to such a rhythm. I have been unable to find an example of this in the literature, but Dr. Ritchie has kindly permitted me to mention an unpublished tracing of his, in which there was a gradual lengthening of the a–c interval until, at every fourth auricular systole, there was a complete a–v block. An extra-systole followed by a compensatory pause, and recurring after every second normal beat, is a common form of triple rhythm. The tracings [1] from the following two cases illustrate this. In both cases the extra-systoles are of ventricular origin.

Case I. A man, aged 52 years, was admitted to Ruchill Hospital on January 6, 1910, with the diagnosis of enteric fever. The patient, who had not been feeling well for about a month before admission, had been confined to bed for the previous week with sickness, vomiting, and pain in the back and abdomen. Until the onset of his present illness he had not suffered from any serious illness, but he had led a hard life as a sailor, and had at times taken alcohol to excess.

On admission the patient, who was moderately nourished and looked much

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[1] All the tracings were taken with Mackenzie's small polygraph with Bigg's time-marker. This time-marker is worked by a separate clockwork from that which moves the paper.

older than his years, seemed somewhat ill and complained of pain in the region
of the left loin. The heart was slightly enlarged, the apex beat being in the
fifth intercostal space, 3½ inches from the middle line; the sounds were pure,
but the second aortic sound was somewhat accentuated; the superficial vessels
were hard and tortuous; the pulse was regular. There was evidence of slight
bronchitis at the bases of both lungs. There was tenderness of the abdomen
with slight rigidity of the muscles over the left renal region, but no tumour
could be felt. Pus was present in the urine. The Widal reaction was positive.
Throughout his residence in hospital the patient had numerous attacks of fever
with vomiting and pain in the left loin; the attacks lasted as a rule for about
twenty-four hours. The pulse was first noticed to be irregular on February 2,
and from then till he left the hospital there were periods of marked irregularity
alternating with periods, often lasting for a day or two, when the pulse pursued
an absolutely regular rhythm. The pulse-rate varied between 102 per minute
during attacks of fever and 72 during the afebrile periods. There were no
definite signs of cardiac failure, though the first sound was somewhat poor in
quality. From February 10 till March 3 tincture of digitalis was given in ten-
minim doses three times a day, but did not seem to have any effect on
the irregular action of the heart. On February 23 bacilli of the coli group
were cultivated from a catheter specimen of the urine and a vaccine made from
this organism. This was given at intervals of seven days in increasing doses,
but without any effect on either the intermittent fever or the pyuria.

The patient was dismissed from hospital on May 14, 1910.

Case II. A boy, aged 2½ years, was admitted to Ruchill Hospital on
February 11, 1910, suffering from a typical attack of measles with slight
broncho-pneumonia. On February 17 the temperature and respirations became
normal and remained so throughout the remainder of the illness. On February 24
the right ear began to discharge; this ceased on March 5. On March 1 the
pulse was noticed to be irregular. The heart was not enlarged, the apex beat
being 2¼ inches from the middle line, the left border of cardiac dullness 2½ inches
from the middle line, and the right border ¼ inch to the left of the middle
line. The heart's sounds were normal. From March 1 until the patient was
dismissed the pulse always presented the same form of irregularity, two normal
beats being followed by a ventricular extra-systole. Respirations had no effect
on the rhythm (*vide* Fig. 4) and a tracing taken while the child was asleep
showed the same form of irregularity.

The child was dismissed well on March 19, 1910, the pulse still remaining
irregular.

This case is also of interest, as extra-systoles occurring in such a youthful
patient seem rare.

Reference to some of the recent literature shows that regularly recurring
ventricular extra-systoles frequently give rise to triple rhythm. Although
no attempt has been made to review the whole literature, examples are given
by Mackenzie (8 and 9), Hay (3), Lewis (7), and Wenckebach (11), and owing
to the kindness of Dr. Cowan I have also had opportunity of examining three
unpublished tracings which show the triple rhythm.

In one of Mackenzie's tracings (*Diseases of the Heart*, Plate IV, Fig. 244)
the triple rhythm is interrupted by five regular beats; this point will be
considered subsequently.

All these tracings have certain points in common which seem to afford
a possible explanation of this form of allorhythmia: (1) In all of them the

extra-systoles arise in the ventricles. (2) The extra-systoles do not occur at shorter intervals than 1·5 sec. or at longer intervals than 2·5 sec. (In some of the tracings there is no time record, but it seems probable that the intervals between the extra-systoles lie within these limits.) (3) In each case the rhythm of the extra-systoles is regular.
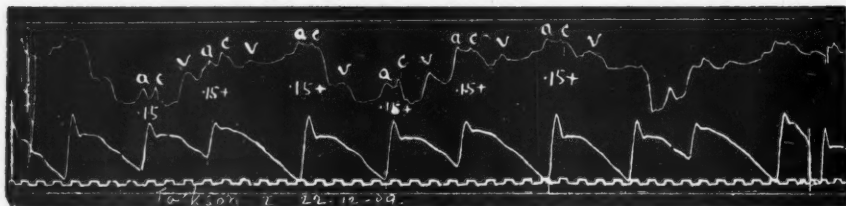

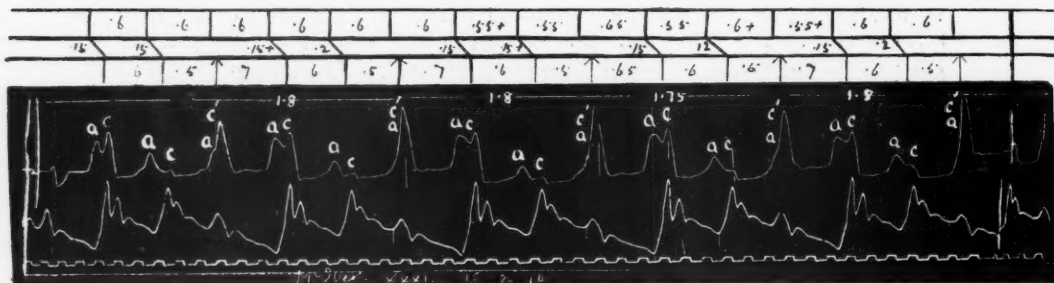FIG. 1. A tracing showing the triple rhythm due to sinus arhythmia. Time marks $\frac{1}{10}$ sec.

FIG. 2. A tracing from the neck and radial artery, showing ventricular extra-systoles occurring about every 1·8 sec. The patient held his breath while the tracing was being taken. Time marks $\frac{1}{10}$ sec.
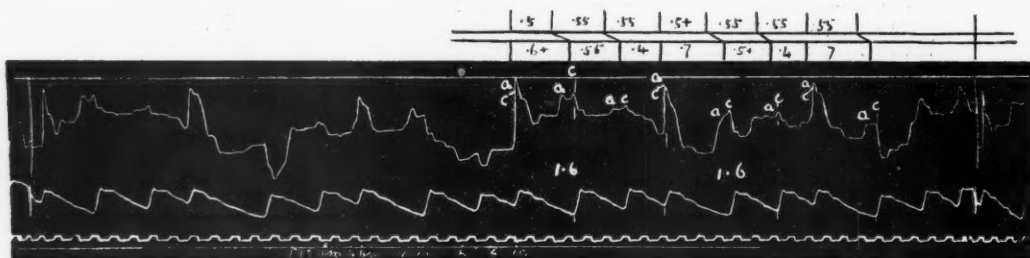
FIG. 3. Tracing from Case II, showing radial and jugulo-carotid curves. Ventricular extra-systoles occur about every 1·6 sec. Time marks $\frac{1}{10}$ sec.

Let us consider tracings Fig. 2 and Fig. 3 respectively. In Fig. 2 ventricular extra-systoles recur regularly every 1·8 sec. and in Fig. 3 every 1·6 sec., that is to say at rates of 33 and 37 per minute. We know from numerous clinical observations that in man the rate of the independently beating ventricle is usually between 30 and 40 per minute, although cases where the ventricles beat much slower, and others where they beat more frequently,
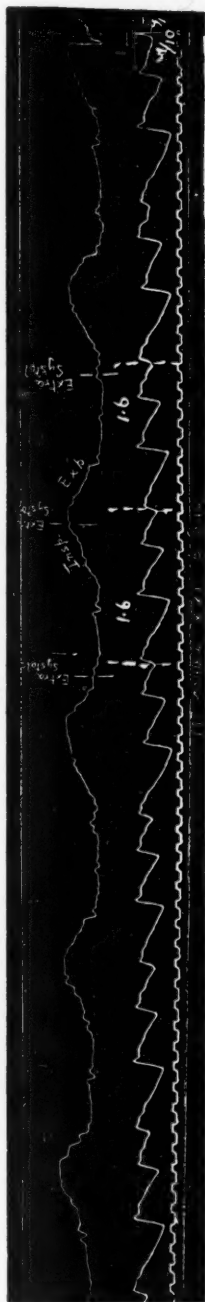
Fig. 4. Respiratory and radial curves taken from Case II. The regularly recurring extra-systoles are seen to occur at all phases of respiration. Figs. 3 and 4 were taken within a few minutes of one another. Time marks $\frac{1}{5}$ sec.

Fig. 5. Shows two extra-systoles with an interval of seven normal beats between them. Time marks $\frac{1}{5}$ sec.

Fig. 6. Radial and jugulo-carotid curves. The pulse, which at the commencement of the tracing shows the triple rhythm, is regular for the last five beats. Time marks $\frac{1}{5}$ sec.

have been reported. This at once suggests that in these two cases, and in the others quoted above, *the ventricles are following a rhythm set by two pacemakers, one at the sino-auricular node, producing physiological beats, and anoth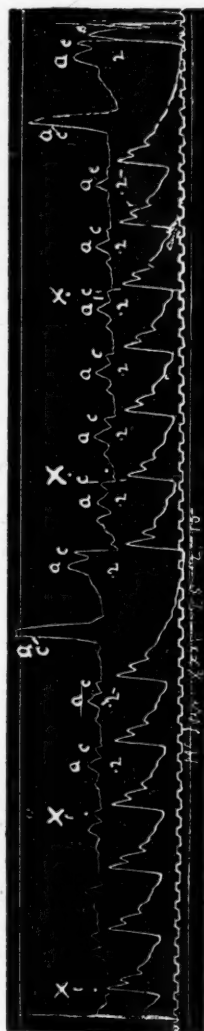er at an irritable focus in the ventricle, which is rhythmically discharging stimuli at the customary rate of ventricular stimulus production, thus giving rise to extra-systoles.*

In Case II very numerous tracings were taken, and they all showed this form of allorhythmia, but in Case I several variations from the triple rhythm were observed; examples of these are shown in Figs. 5, 6, and 7. In Fig. 5 two extra-systoles occur with seven physiological beats between them. In Fig. 6 the triple rhythm abruptly ceases, and in Fig. 7 the extra-systoles gradually become merged in physiological beats, though the change is not complete before the tracing ends.

In Fig. 5 there is an interval of seven physiological beats between two extra-systoles. In this case there are two possible explanations : either stimuli were not arising rhythmically in the ventricle at the usual rate of ventricular stimulus production, or, if they were arising, were not effective. This latter alternative seems quite possible, for if stimuli were arising in the ventricle at intervals of 1.8 sec., i. e. at the usual rate of ventricular stimulus production, they would have occurred at the two extra-systoles and at the points marked X in the tracing; but all the points marked X lie within the sphygmic periods of physiological contractions, and so if stimuli had arisen in the ventricle at these points they would naturally have proved ineffective.

In Fig. 6 ventricular extra-systoles occur at intervals of 1.85 sec., 1.8 sec., and 1.9 sec.; the heart then becomes regular. If an abnormal stimulus were again to arise 1.9 sec. after the last extra-systole, marked (3) in the tracing, it would fall at the point X, i.e. within the sphygmic period of a physiological beat, and so would naturally fail to produce an extra-systole. Here, then, a slight change in the rate of production of abnormal stimuli disturbed the triple rhythm.

In Fig. 7 the triple rhythm almost disappears. In the early part of the tracing the sinus stimuli occur at intervals of 0.65 sec., but in the latter part at intervals of 0.6 sec. When extra-systoles occur in the early part of the tracing the ventricles and auricles contract almost synchronously, but in the penultimate extra-systole the auricular contraction occurs slightly before the ventricular, while at the last (B), which is scarcely recognizable, the ventricular beat being only slightly premature, the sinus stimulus has almost succeeded in anticipating one of the regularly recurring ventricular stimuli. In this case, a slight increase in the rate of sinus stimulus production has almost disturbed the triple rhythm.

Mackenzie (*Diseases of the Heart*, Plate IV, Fig. 244) shows a tracing in which the break in the triple rhythm can be explained in a somewhat similar manner. In this tracing the sinus stimuli arise somewhat irregularly, while the abnormal ventricular stimuli arise almost regularly. In the middle of the

tracing an abnormal stimulus is due to occur during a normal systole; this explains the five regular beats at this point. Three extra-systoles then follow, the first two of which are described as being of auricular origin, but I think it is possible that they are ventricular. A pause in the allorhythmia then ensues, and here again, if the stimulus production in the ventricle continued undisturbed, an extra-systole would be due after 1·9 sec., but at this moment the ventricle has already commenced to respond to the sinus stimulus and so no extra-systole results.

In Case I the patient's heart sometimes beat regularly. It is possible that on these occasions either the irritable focus in the ventricle was silent, or regularly recurring ventricular stimuli were arising during the sphygmic periods of physiological beats. In the tracings showing regular heart's action, every series of three beats occupied about 1·9 sec. So it is possible that during these regular periods ventricular stimuli were arising at their usual rate of 1·9 sec., but that they were all occurring during physiological systoles.

In a recent paper by Cowan and Ritchie (1) an explanation has been suggested for certain forms of coupled rhythm, and this suggestion might be extended to apply to the triple rhythm now under discussion. These authors suggest: 'Whenever an enfeebled heart is unduly irritable in an abnormal site, any excessive rise of intraventricular pressure may produce a regularly recurring premature systole which originates in the irritable area.' Although this suggestion might hold good in the case of the child (Case II), where all the curves show the triple rhythm, it does not seem to explain satisfactorily several of the curves from Case I. It cannot account for tracing Fig. 5, where there is a series of seven normal beats between two extra-systoles, neither does it explain Fig. 7. In this tracing five regularly recurring extra-systoles are seen. At the extra-systole marked A in the tracing the auricles and ventricles contract synchronously, while at the extra-systole marked B the auricular wave precedes the 'c' wave in the phlebogram by about 0·15 sec., that is to say the auricle contracts before the ventricle. The pressure within the ventricle immediately before the extra-systole at A must be much less than the pressure within the ventricle immediately before the extra-systole at B, for at A the ventricle has not received any blood from the auricle before it contracts, while at B the auricle must have expelled some of its blood into the ventricle before the ventricular contraction takes place. From this it seems probable that the occurrence of extra-systoles in this case is not due to conditions of intraventricular pressure.

Although the suggestion brought forward in this paper has been limited to the explanation of triple rhythms due to ventricular extra-systoles, it might be extended to account for the occurrence of various forms of allorhythmia due to extra-systoles; an example may be seen in a tracing shown by Mackenzie (10), where a ventricular extra-systole occurs after every physiological beat. Others are shown by Hay (4), where nodal extra-systoles occur after each normal beat, by Hay (5), where ventricular extra-systoles occur after every third normal

beat, and by Laslett (6), where extra-systoles, though sometimes interpolated and sometimes followed by a compensatory pause, still pursue a constant rhythm.

The explanation of rhythmically recurring extra-systoles suggested in this paper raises a point of some interest as regards the method of production of stimuli in the heart. Stimulus production may be (1) a continuous process, or (2) a discontinuous process.

1. If it is a continuous process the explanation of the rhythmical recurrence of extra-systoles given in this paper cannot be correct; for if the ventricles were continually being stimulated by an abnormal stimulus-producing centre an extra-systole would occur whenever the other properties of cardiac muscle—excitability, conductivity, and contractibility—were in a condition to respond to stimuli. But in all these cases of triple rhythm these properties were active at least seventy times a minute, whereas the heart responded to abnormal stimuli not more frequently than forty times a minute.

There is some experimental evidence that the production of stimuli is not a continuous process. If a ventricle be made to respond rhythmically to a continuous stimulus, and then an extra-systole be produced, it is not followed by a compensatory pause and the rhythm produced by the continuous stimulus is unaltered. This shows that if the physiological stimulus were continuous an extra-systole would not be followed by a compensatory pause (2).

2. Stimulus production may be a discontinuous process. In this case it is possible that stimuli may either arise gradually after each systole, or suddenly immediately before a systole occurs. If after each extra-systole in a case of triple rhythm stimuli were to arise gradually at an irritable point in the ventricle, one would expect that the more frequent physiological systoles would interfere with the gradual and less frequent formation of abnormal stimuli. This apparent difficulty might be explained by supposing that the irritable focus in the ventricle, which gives rise to rhythmic extra-systoles, lies in what may be called a backwater of the primitive cardiac tissue, and while stimuli can stream down this backwater, physiological stimuli passing down the main channel are unable to disturb the point where ventricular stimuli arise.

If on the other hand we suppose that stimuli are produced suddenly immediately before each cardiac systole, it is possible that stimuli, arising suddenly at an abnormal point in the ventricle, would produce a rhythm uninterrupted by the physiological contraction of the heart, and that extra-systoles would result so long as these rhythmically produced abnormal stimuli occurred during the diastole of the heart and when the other properties of the cardiac muscle were sufficiently restored to enable it to respond to such a stimulus. Diagrams 8 and 9, which have been modified from diagrams of Wenckebach (12), represent the gradual and sudden formation of stimuli. The thin ascending lines represent the formation of stimuli at the sinus, the thick ascending lines the formation of stimuli in the ventricle, the descending interrupted lines the gradual lowering of the 'threshold of excitability'. In Fig. 8 stimulus production is represented as gradually increasing until it meets the

FIG. 7. Curves from radial artery and jugular vein. The pulse almost becomes regular towards the end of the tracing. Time marks $\frac{1}{10}$ sec.

FIG. 8.

FIG. 9.

interrupted line representing excitability; at this point a systole occurs, stimulus production falls to zero, and the threshold of excitability rises to infinity. An extra-systole results whenever a stimulus arising in the ventricle is able to effect excitability before the physiological stimulus acts. Such a condition is represented at the points marked R in the diagram. In Fig. 9 stimuli are represented as arising much more suddenly; in this case the physiological systoles would not interfere with the production of abnormal stimuli, but in Fig. 8 the systoles resulting from the normal stimuli might be expected to interfere with the formation of abnormal stimuli.

With our present knowledge of the physiology of the heart's action it is impossible to say whether either of these suggestions is the true explanation of the irregularities shown in the tracings. Nevertheless there can be no doubt that some of the tracings show that stimuli were arising rhythmically in the ventricles and that the physiological heart-beats did not interfere with this abnormal process.

It must be admitted that there are certain tracings in the literature in which fairly regularly recurring extra-systoles occur which cannot be explained by the above suggestion (e. g. Mackenzie, *Diseases of the Heart*, p. 322, Fig. 227, and Plate III, Fig. 242), but if we take into consideration the striking way in which it can be employed to explain not only many cases of triple rhythm, but also many cases in which this rhythm is not constant, the rhythmic production of stimuli at an abnormal site seems to be an explanation of various forms of cardiac allorhythmia which is worthy of further attention and investigation.

I have much pleasure in expressing my thanks to Drs. Cowan and Ritchie for much valuable advice and assistance.

Summary.

Tracings from two cases showing regularly recurring ventricular extra-systoles are discussed. It is suggested that the rhythmical production of stimuli at an abnormally irritable point in the ventricles may produce such rhythmic irregularities.

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A NOTE ON THE DIAGNOSIS OF SINUS ARRHYTHMIA

By J. DAVENPORT WINDLE

It is a well-known characteristic of sinus arrhythmia that the irregularity usually disappears under circumstances which quicken the heart; during a febrile attack, for instance, the rhythm continues quite regular so long as the pulse rate is above the normal, but when the heart slows again the irregularity recurs and is often more pronounced than before.

The fact, however, is not generally recognized that, particularly in children, sinus irregularity may occur for the first time coincidently with the marked slowing of the pulse which is so frequent during the early stages of convalescence from the acute infections. When the condition is for the first time detected under these circumstances—which it frequently is—its significance is liable to be misunderstood, for in some cases the irregularity is of high grade, and may readily arouse suspicion of serious heart trouble. It is, however, now well established that sinus irregularity in itself has no unfavourable prognostic significance, whatever the conditions may be under which it occurs—but rather the contrary; there are many reasons which support the view advanced by Mackenzie(2) that it is evidence of a healthy heart muscle; for the present purpose it suffices to state that it has not yet been shown to occur in degenerative heart lesions. Sinus irregularity can as a rule be readily identified by ordinary methods of clinical examination; in cases of doubt the diagnosis is usually at once established by records of the pulses and respiration. Exceptionally, however, difficulty arises and it becomes a question whether the irregularity may not be due to some other cause. In a previous communication (3) I directed attention to possible fallacies in the interpretation of the pulse records in cases where the diastolic b-wave described by Gibson of Oxford (1) is present in the venous pulse. It was shown in the cases observed that this wave was present in the curve during the longer diastolic phases alone, being differentiated with pulse periods at a rate below 80 per minute, but with cycles above this rate the wave disappeared from the tracing or blended with the succeeding a-wave, and gave rise to an apparently lengthened intersystolic interval, and further that the wave might recur in an apparently mid-position between the preceding and following a-waves and thus closely simulate partial heart-block.

A further element of confusion in diagnosis is the occurrence in some cases of an additional heart sound coinciding in the cardiac cycle with the b-wave.

Both these events are the result of a simple physiological mechanism, namely, diastolic closure of the auriculo-ventricular valve at the end of ventricular filling; the flow from auricle to ventricle is suddenly checked and a reflux occurs into the jugular vein—the *b*-wave. Exceptionally, the closure of the valve is sufficiently vigorous to cause a sound—the third heart sound. The sudden apposition of the cusps requisite for the production of the sound is only possible with rapid and complete ventricular filling, and in order to this a certain length of diastole is necessary; if the heart's action is quick, systole occurs before the ventricle is completely filled.

It follows that when the heart is irregular the third sound will only be heard with the slower beats, and unless its cause is recognized the sound may be readily ascribed to some pathological condition.

In the following case marked irregularity of the heart was present and the sounds with some of the beats were unusual. The diagnosis was of importance from the clinical circumstances attaching to the case, which, as will be seen, illustrates very well the value of graphic records in clinical work.

A girl aged 5 had an attack of scarlet fever of moderate severity which ran its course without any untoward symptom until the febrile stage was over, when for the first time the pulse was noticed to be irregular. This symptom gave rise to anxiety, being regarded as an indication of probable heart failure. In spite of well-directed treatment the irregularity persisted, and it was further noticed that the heart sounds were abnormal. When I saw the patient her general condition appeared good; no symptoms were present calling for note, and no signs of disease except irregularity of the heart, which was very pronounced (Fig. 1). It was readily determined that the changes in rhythm synchronized more or less with the respiratory movements, the longer pauses occurring during expiration, but not constantly so. When the breath was held the irregularity was less marked, and at times, but not always, the pulse became quite regular and slow during suspension of breathing (Fig. 2). With forced breathing the pulse quickened but continued irregular, and this was the case after the exertion of quickly sitting up in bed and lying down again a few times. It was concluded that the irregularity was of sinus origin, but on listening to the heart doubt at once arose, for while the sounds with the quicker beats were normal, three well-marked sounds were heard with most of the slower beats; constantly with these during expiration, but not when the slowing occurred during inspiration. The additional sound was best heard in the neighbourhood of the impulse with the patient lying down; it was not audible over the base of the heart, or in the neck, nor when she was sitting up. It closely resembled the first sound, but was of slightly higher pitch and was not so loud or long, although clearly struck. It occurred after an interval approximately equal to that between the first and second sounds. It did not give the impression of a double second sound occurring later than a duplication would be expected, and there was nothing in its character to suggest a diastolic murmur. On the whole it was very like the single sound which occasionally accompanies an
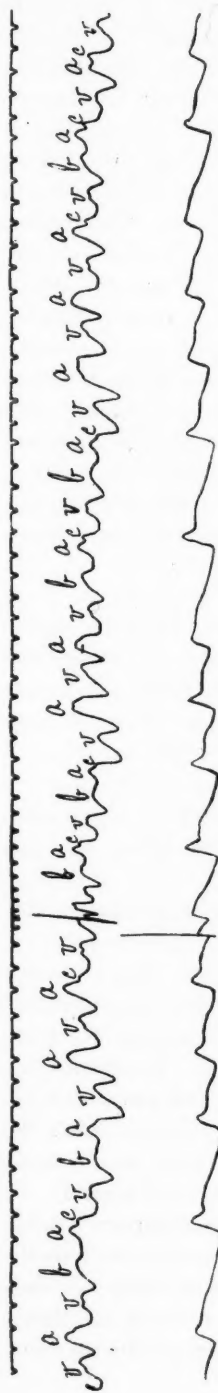
FIG. 1.   Tracing of radial and venous pulses, from the case described in the text.   The irregularity is of sinus origin ; with the quicker beats two waves, a and v, are present ; with the slower beats waves a and c are differentiated and an additional wave, b, is present between v and a.   The large size of a with the quicker beats is due to blending of the waves b and a ; the a–c interval is less than $\frac{1}{5}$ sec.

FIG. 2.   Tracing of the respiratory movements of the chest and radial pulse, from the same case as Fig. 1.
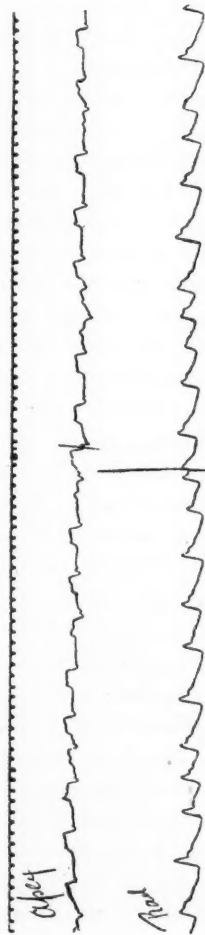
FIG. 3.   Tracing of the apex beat and radial pulse, from the same case as Figs. 1 and 2.   The curves coincide.

extra-systole ; although no corresponding cardiac impulse could be detected this
cause could not certainly be excluded, since very exceptionally extra-systole
may occur without any perceptible movement of the heart. A tracing of the
apex beat and radial pulse is shown in Fig. 3. The diagnosis thus lay between
a condition of partial heart-block, with an auricular sound, extra-systoles, or
sinus irregularity with a sound due to diastolic closure of the a–v valves.
A venous tracing was obtained with some difficulty because of the shortness of
the neck, and restlessness of the patient.   Fig. 1 is a record from visible venous
pulsation on the left side of the neck, and the radial pulse.   With the quicker
beats two waves, a and v, only are present; during the longer pulse periods
waves a, c, and v are evident, and an additional wave (b) occurs between
v and a.   The apparently lengthened a–c interval and large size of a with the
quicker beats is due to fusion of b and a and not to impaired conductivity, since
where b, a, and c are differentiated the a–c interval is less than 0·2 sec.   The
wave b is evidently not due to independent auricular contraction or extra-
systole of either chamber; its time relationships clearly establish its identity ;
moreover the third heart sound was heard only with those beats in which this
wave was present, and so far as could be estimated the additional sound
synchronized with the position of the wave in the cardiac cycle.

Analysis of the venous tracing thus proves the mechanism of the heart
to have been in all respects normal, and that the irregularity was solely due to
lengthening and shortening of the diastolic phases.   The more or less definite
coincidence of the changes in rate of the heart with the respiratory movements
established the diagnosis of sinus arrhythmia.   The high grade of irregularity
present furnishes all necessary factors for a diastolic closure of the tricuspid
valve sufficiently sudden to send a wave back into the jugular vein and cause
a sound, for during the long pauses there must have been relatively high venous
pressure which conduced to complete and rapid ventricular filling, and this
in turn to vigorous apposition of the cusps.

I venture to say that in this case a myocardial lesion as the cause of the
irregularity could not have been excluded without the aid of pulse records.   It
is needless to emphasize the importance of the diagnosis further than to remark
that such a high grade of irregularity, had it been due to extra-systoles or partial
heart-block, would have indicated a very serious condition, calling for strict
and prolonged treatment.   That the conclusion reached was the correct one
is evidenced by the subsequent history of the case ; treatment was suspended,
in a few days the patient was out of bed, and convalescence was uneventful.   No
symptoms whatever referable to the heart have since occurred at any time,
although the irregularity and its accompaniments as described still persist.

During many years' charge of isolation wards I have found sinus arrhythmia
the most frequent form of irregularity in children during convalescence from the
acute infections.   In many patients it is present only during sleep, and then
sometimes to a very high degree ; the probable explanation being the slower
breathing and pulse rates during sleep.   In other cases the irregularity continues

so long as the patient is kept in bed, but disappears on getting about again, but at times I have observed the irregularity persist for months subsequent to its first appearance during convalescence.

The case described in the text is the only one coming under my notice with a third heart sound, but the *b*-wave is frequently present in cases in which the degree of irregularity is great, and I again emphasize the remarkably close likeness which such a tracing may bear to one of impaired conductivity and partial heart-block. Again, in some cases of sinus arrhythmia there is marked sudden slowing of the last beat of a group, recurring regularly with expiration ; not infrequently rhythmic extra-systoles show the same respiratory relationship, and the distinction between the two conditions is at times difficult. An instance
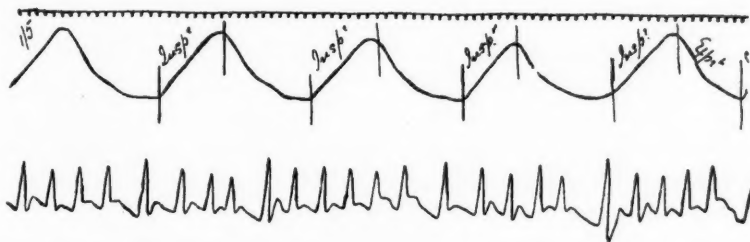

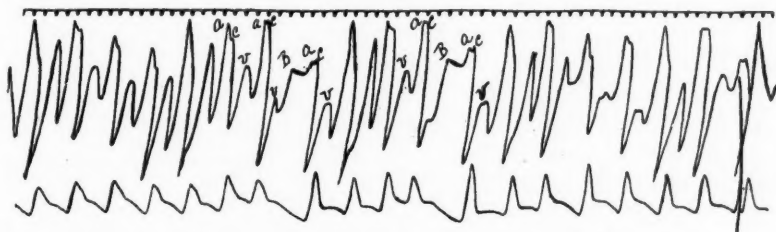FIG. 4. Tracing of the respiratory movements of the chest and radial pulse.

FIG. 5. Tracing of the jugular and radial pulses from same case as Fig. 4. It is a question whether the two beats with the long pauses are due to auricular extra-systoles.

is illustrated in Fig. 4, which is a record of respiratory movements of the chest and radial pulse taken from a youth of 15, after a febrile attack with sore throat of doubtful nature. The longest pulse pauses coincide with the expiratory phases of respiration, and to the finger the irregularity was very like that due to extra-systoles. The degree of sinus arrhythmia present renders the interpretation of the venous pulse obscure (Fig. 5). The possibility that the waves succeeding the *b*-waves in the longest pulse pauses may be due to auricular extra-systole cannot certainly be disproved by measurement, but the character of the tracing as a whole strongly militates against this view. Moreover, the sounds of the heart with the slower beats were of full strength and equally spaced ; there was not the characteristic grouping usually heard with extra-systole. No murmurs were present and the absence of enlargement of the heart was a

further fact supporting the diagnosis of sinus arrhythmia, since in cases under my notice of definite extra-systole in children and young people occurring subsequent to an acute illness I have always found the heart enlarged. On the contrary, sinus arrhythmia is not associated with an enlarged heart under these circumstances—that is to say, sinus arrhythmia and extra-systole would appear to be incompatible. The case has been kept under observation for over two years subsequent to taking the record shown in Fig. 4. The irregularity has persisted, being found sometimes slight, at others extreme; the condition of the heart has continued to be in all respects normal.

Summary.

Irregularity of the heart in children during convalescence from febrile illness is common. In some cases it results from arrhythmic contraction of the heart's chambers or disturbance in the conduction of impulses from auricle to ventricle—conditions which evidence disease of the myocardium and are of serious prognostic import; but in the majority of cases the irregularity is solely due to variations in length of the diastolic phases of the cardiac cycle, while in all respects the heart's mechanism is normal—sinus arrhythmia—a form of irregularity which is devoid of any pathological significance whatever.

The frequent occurrence of sinus arrhythmia after acute illness in children is not generally known to practitioners, and the irregularity is confused with those of pathological origin. Its recognition is important, otherwise the patient is needlessly kept in bed and subjected to unnecessary treatment until it becomes manifest that the irregularity is a negligible symptom.

While as a rule the diagnosis of sinus irregularity is readily made on clinical examination, exceptionally it is only established from records of the heart's movements and respiration. The cases described in the paper illustrate possible fallacies in the interpretation of tracings.

REFERENCES.

1. Gibson, A. G., *Lancet,* Lond., 1907, ii. 1380.
2. Mackenzie, James, Personal communication.
3. Windle, J. D., *Quart. Journ. Med.*, Oxford, iv. 383.

THE ORIGIN OF PREMATURE CONTRACTIONS

By THOMAS LEWIS[1] AND M. D. SILBERBERG

(From University College Hospital Medical School)

With Plates 16 and 17

DURING the systematic examination of patients, the subjects of irregularity of the heart's action, the mechanism in a large number of such patients is found to result from premature contractions arising in one or other heart chamber. Thus the premature beat may arise in auricle or ventricle. The origin of beats in auricle or ventricle may be identified by means of the polygraph, and a wide experience shows that with few exceptions a patient, who exhibits irregularity of the heart, maintains the same type of irregularity from time to time while under observation. The majority of people, who persistently demonstrate premature contractions, are found to have premature auricular or premature ventricular contractions, respectively, and in most cases the types are not mixed in the same case.

Electro-cardiographic examination of the same patients permits a nicer localization of the points of origin of the premature beats. It may be taken as a general rule that the outline of the electro-cardiographic curve, whether it is associated with an auricular or with a ventricular beat, is an index of the direction taken by the contraction wave in the corresponding musculature. It is consequently an index of the points of origin of such contraction waves. Now, premature contractions give rise to electric curves, which, when compared with those of the rhythmic beats, are usually of anomalous form, and the variation in the types, found in conjunction with premature contractions arising in auricle or ventricle respectively, is considerable. The association of the particular anomalous complex with the point of origin of the beat to which it is due is not fully understood ; that is to say, the points of origin cannot be accurately located at the present time ; but this minute localization does not concern us. We are content to start from the conclusion that in a single patient a given type of electric complex represents a definite course of the contraction wave, and that such a complex indicates the origin of the contraction at a definite point or in a definite area, known or unknown.

Our observations were made to determine the constancy or inconstancy of

the position of a point or area giving rise to premature contractions in cases examined from day to day, week to week, or year to year.

For if we could show that the type of electric complex accompanying premature contractions in a given case was of fixed form, from time to time, we should have strong presumptive evidence that the site of irritation remained limited for more or less prolonged periods.

We have examined a large number of patients from this point of view and have compared the electro-cardiograms taken on several or many occasions from these cases. For the most part we have adopted one lead, but often we have employed two or three leads and have been able to compare the curves given by such leads on two or more occasions.

Our results are embodied in the following paragraphs, which treat of nine patients. In each instance we have briefly described the type of electric curve obtained and have given the dates upon which the curves were taken and the leads which were adopted. The leads are referred to as I, II, and III; these represent leads from right arm to left arm, right arm to left leg, and left arm to left leg, respectively.

Cases with premature auricular contractions.

Case I. T. M. Premature auricular contractions. The premature beat at each examination showed P inverted and of identical form in lead II. P was constantly iso-electric in lead I. The patient was examined on at least seven occasions: 28/8/10, lead II; 3/9/10, lead II; 8/9/10, leads I and II; 10/10/10, lead II; 1/4/11, lead II; 16/6/11, leads I and II; 18/6/11, leads I and II; 5/11/11, leads I and II. Sample curves are shown in Figs. 1 and 2.

Case II. H. B. Premature auricular contractions. The auricular representative of the premature contraction retained a constant form for a given lead throughout all examinations. Lead I showed P almost iso-electric; lead II showed P inverted; lead III showed a small inverted P. The patient was examined on twenty or thirty occasions. We have dated curves as follows: 13/7/9, lead II; 28/1/10, lead II; 22/4/10, lead II; 16/12/10, leads II and III; 18/3/11, leads I, II, and III; 25/3/11, leads I, II, and III; 30/3/11, leads I, II, and III.

Case III. C. Premature auricular contractions. The auricular representative of the premature contraction was of constant form, it was much smaller than the normal auricular summit, and there was a deeply cut notch at its apex. The patient was examined on the following dates: 2/4/11, lead II; 19/5/11, lead II.

Cases with premature ventricular contractions.

Case IV. A. M. Premature ventricular contractions. The premature ventricular complexes were of the same general form as those of the rhythmic beats; and this statement applies to the usual three leads adopted. The premature beats probably originated in the a-v bundle (*Quart. Journ. of Med.*, 1911, v. 1). Precisely the same pictures were obtained in each separate lead on the several occasions. The patient was examined on the following dates: 2/3/10, lead II only; 24/3/11, leads I, II, and III; 19/5/11, leads I, II, and III.

Case V. G. P. Premature ventricular contractions. The premature ventricular complex was of the form usually recognized as associated with beats originating in the left or apical portion of the ventricular musculature. Curves were taken from lead *II* on the following dates: 19/11/8, 9/6/9, 3/2/10; leads *I, II*, and *III* were used on 17/9/10. On each occasion precisely similar types of premature ventricular complexes were obtained for lead *II*. It is to be noted that the interval between the first and last record extended over a period of nearly two years.

Case VI. L. L. Premature ventricular contractions. In this case the premature ventricular complexes were of the form usually recognized as associated with beats having their origin in the right or basal portion of the ventricular musculature. Curves were taken on 21/9/10, lead *II* only; 8/4/11, leads *I, II*, and *III*; 14/6/11, leads *I, II*, and *III*. The type of the premature contraction was the same on each of these dates.

Case VII. R. D. Premature ventricular contractions. The premature ventricular complexes were of the form usually recognized as associated with beats originating in the left or apical portion of the ventricular musculature. The patient was examined on two occasions: 26/5/10, leads *I, II*, and *III*; 24/3/11, leads *I, II*, and *III*. The corresponding leads gave identical pictures on the two occasions.

Case VIII. J. B. Premature ventricular contractions. The premature ventricular complexes were of the form usually recognized as associated with beats arising in the right or basal portion of the ventricular musculature. The patient was examined on four occasions: 3/9/10, lead *II*; 29/3/11, leads *I, II*, and *III*; 17/5/11, leads *I, II*, and *III*; 9/6/11, leads *I, II*, and *III*. Corresponding leads gave similar pictures on all occasions. Sample curves are shown in Figs. 3–9.

Case IX. M. F. Premature ventricular contractions. The premature ventricular complexes were of the form usually recognized as associated with beats originating in the left or apical portion of the ventricular musculature. Curves were taken on 12/12/10, lead *II*; 5/4/11, leads *I, II*, and *III*; 8/6/11, leads *I, II*, and *III*. The corresponding leads gave identical pictures on these three occasions.

Discussion.

We may summarize the results of the examination of these patients. There are three cases in which premature auricular contractions are shown. The electric representatives (*P*) of the premature contractions remain constant in form upon repeated examination. In illustration of this statement we publish Figs. 1 and 2, curves which were taken from Case I. Each figure shows a rhythmic beat (*P, R,* and *T*), and following upon the rhythmic beat is a premature beat, which is of similar form to the former, but differs from it in that *P* is inverted. The outline of *P*, the representative of the premature auricular contraction, and a contraction which has taken an abnormal course in the auricle, is the same in the two curves, though Fig. 1 was obtained on August 28, 1910, and Fig. 2 was obtained on June 16, 1911, ten months later. We conclude

that the focus of irritation has remained constant in this patient over the period named.

There are six cases in which premature ventricular contractions are shown. Repeated examination has demonstrated that the electric curves corresponding to the abnormal ventricular beats retain their distinctive outlines in each instance. In illustration of this statement we publish Figs. 3–9, a series of curves taken from Case VIII. Fig. 3 shows two cycles (P, R, and T) belonging to the normal and rhythmic series, and one premature ventricular cycle, which is complicated by the sequential auricular beat (P) falling with it. Lead II gave this curve, which was taken in September, 1910. Curves, from the same lead and patient, are shown in Figs. 5 and 8; they were taken on March 29, 1911, and May 17, 1911. The pictures are similar; they differ only in small variations in amplitude and as a result of the inconsistency of time-relation between the abnormal ventricular complex and the sequential P which falls with it. Thus the abnormal complex in Fig. 5 has, as usual, a bifurcated summit, but the first point of the summit is proportionately higher than in Figs. 3 and 8 because P has fallen with it and is superimposed upon it. Fig. 4 is a curve taken from lead I on March 29, 1911; Fig. 7 is from the same lead on May 17, 1911. The abnormal ventricular beats are of similar outline. So also in the curves of lead III; Fig. 6, taken on March 29, 1911, demonstrates the same type of curve as does Fig. 9, taken on May 17, 1911. We conclude that the focus of irritation, in this instance a ventricular one, has remained constant in this patient.

Precisely similar results have been obtained in each and all of the cases examined, and the same conclusion applies to them; and, as there has been no exception in the series cited and no exception in a number of other cases in which similar observations have been made, we are able to formulate the general conclusion that in patients who exhibit premature contractions, the site of impulse formation, or focus of irritation, tends to be constant from day to day, from week to week, from month to month, and even from year to year.

We believe that this conclusion is of importance, for in many of the patients there has been reason to suspect widespread affection of the musculature, yet each patient has shown but a single and constant focus of irritation. We are led, from this observation alone, to the belief that the focus of irritation has its seat, not in the general musculature, but rather in some specialized tissue or some tissue which reacts to disease in a special manner. For it is difficult to believe, if the site of irritation is the general muscle wall itself, that the irritable focus should be so sharply limited, considering that there is strong presumption that the damage to this muscle is widespread. In coming to this conclusion our thoughts turn naturally to the special tissue which forms the junction between auricle and ventricle. Now the premature contractions seen in the six patients, in whom the focus of irritation lay below the auricle, have been of three types, and three types only. The largest group of cases has shown a type of beat which is recognized as specially associated with the right side of the heart (Figs. 3–9); the second group has exhibited a type of beat specially associated with the left

side of the heart; a third group (a single case, Case IV) has shown a type of beat which almost certainly originated in the junctional tissues, and probably in the main stem of the auriculo-ventricular bundle. Again, the types of curve corresponding to or associated with irritation on the right or left side of the heart are by no means incompatible with the origin of the respective beats in the right and left divisions of the main bundle. The types of curve yielded by impulses travelling along right or left branches alone are known; and, in so far as they are known, they are similar to those which are found in these cases of premature contraction. Moreover, the statements which we have made may be extended to a far larger collection of curves in our possession. With but few exceptions, the types fall into the three groups mentioned; the right type still forms the largest group, the left type forms an almost equally large group, and the third group consists of three similar cases of premature contractions arising in the main stem of the junctional tissues. We can see no evidence opposed to the conclusion in the curves published by other observers, but rather find support in them.

It is true that there are solitary instances which do not conform to the types mentioned; they are rare and isolated, and their occurrence does not invalidate the conclusion to which we lean, namely, that the majority, if not all premature ventricular beats, arise in the special system of junctional tissues.

This conclusion is not new; it was brought forward by Mackenzie in this Journal (*Quart. Journ. of Med.*, 1907–8, i. 131) some years ago, and the main evidence which we find in his paper in favour of it is the occasional origin of premature contractions which are localized as arising in the auriculo-ventricular node. It is important that it should not be regarded as in any way a fixed conclusion; we regard it as a point of view which may be held, one which is compatible with our present information, but which still requires the support of far more evidence than we are able to supply at the present time. The conclusion to which we desire to draw special attention is that which emphasizes the constancy of the focus of origin in a single patient from time to time.

Conclusions.

1. The electric curves of premature contractions obtained in repeated examinations of the same patients show a remarkable constancy of outline; this fact is regarded as evidence of the constancy and limitation of the focus of irritation in which they are produced.

2. There are facts which suggest, but do not allow us to conclude finally, that premature ventricular contractions arise as a rule in the special tissues which unite the auricular and ventricular musculature.

DESCRIPTION OF FIGURES.

Figs. 1 and 2. Two electro-cardiograms from Case I, lead *II*; taken on August 28, 1910, and June 16, 1911, respectively.

Figs. 3 to 9. Seven electro-cardiograms from Case VIII. Figs. 3, 5, and 8 were taken from lead *II* in September, 1910, and on March 29, 1911, and May 17, 1911, respectively. Figs. 4 and 7 were taken from lead *I* on March 29, 1911, and May 17, respectively. Figs. 6 and 9 were taken from lead *III* on March 29, 1911, and May 17, respectively.
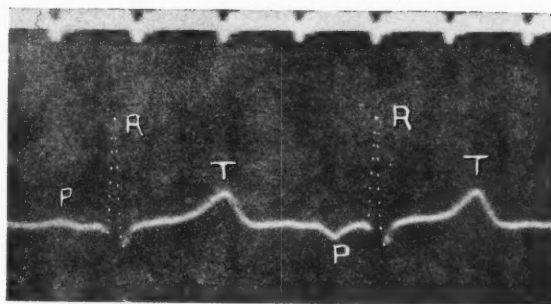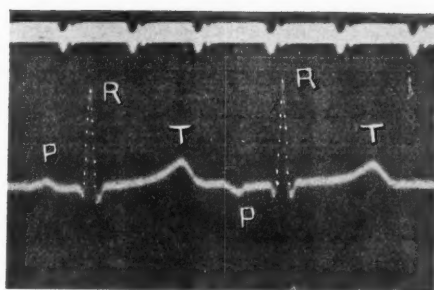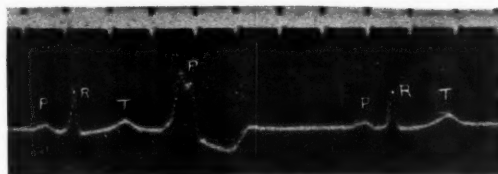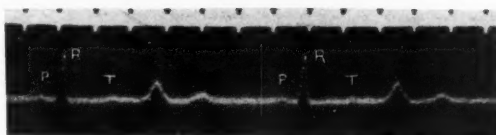
FIG. 1

FIG. 2
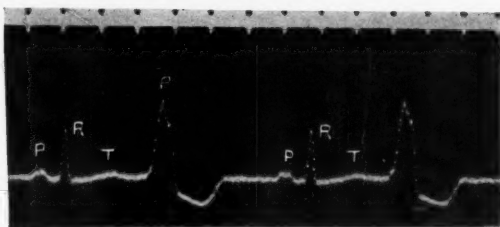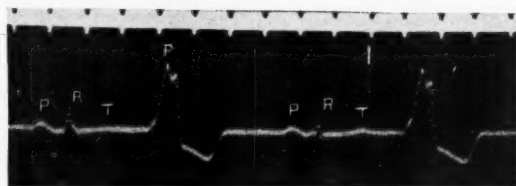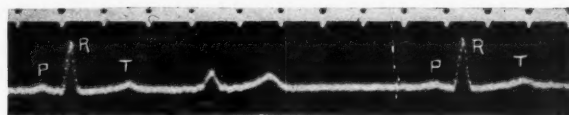

FIG. 3
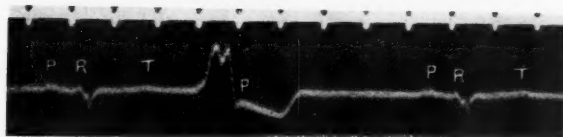

FIG. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Fig. 9

BLOOD-PRESSURE VARIATIONS ASSOCIATED WITH LUMBAR PUNCTURE, AND THE INDUCTION OF SPINAL ANAESTHESIA

By H. TYRRELL GRAY AND LEONARD PARSONS

THIS paper gives a few of the results obtained in the course of a prolonged research into the variations of blood-pressure occurring during surgical operations; the mechanism of such changes; and their relationship to the development of the condition known as 'Surgical Shock'. The clinical results have been arrived at by means of an apparatus specially devised for this investigation, and made for us by Mr. Hawksley; these results have, in addition, been largely confirmed by experiments on animals. In the first place, therefore, a brief description of the apparatus employed is desirable.

I. *Description of the form of Clinical Apparatus employed.*

In all estimations of blood-pressure, and in particular for the purposes of this research, an apparatus giving a graphic record has far greater value than the ordinary form of Riva-Rocci instrument: of such a type, the two best known instruments are Gibson's and Erlanger's. Isolated readings every two or three minutes are of very little value in an accurate investigation of blood-pressure changes, for all our researches show that the blood-pressure is never constant, but varies between relatively wide limits (10–20 mm.) in a short interval of time. Further, the comparison of clinical results with animal experiments is only really possible when we have a clinical apparatus that gives a continuous record of blood-pressure, since that is the condition which obtains in the latter. It is of course impossible to get an absolutely continuous blood-pressure trace in man; but, by means of the apparatus we have devised, a graphic record can be obtained every ten seconds. Such a trace gives as near an approach to a continuous reading as is possible in man. In addition our apparatus gives continuous records of pulse and respiration: and the length of time over which such records can be taken is about three hours.

As a basis for our machine we have used G. A. Gibson's excellent apparatus, which is too well known to need a detailed description here. We regard it as the most accurate blood-pressure machine available for clinical purposes. We have replaced the smoked recording surface by paper and used writing pens on

the recording levers. The rod (*a*) in Fig. 1, which holds the tambour and lever for the pulse trace, has been continued upwards to a point above the level of the drum, and united by a bar to the main column to ensure rigidity. This rod carries two other tambours and levers; one of these is used to obtain a respiratory trace, and the other to obtain an uninterrupted record of the pulse from the other arm. Each of these three tambours can be moved up or down the rod.

In addition to the style (*b*, Fig. 1) which gives the excursions of the manometer (*m*, Fig. 1), there is another small style (*c*, Figs. 1 and 3) which marks the
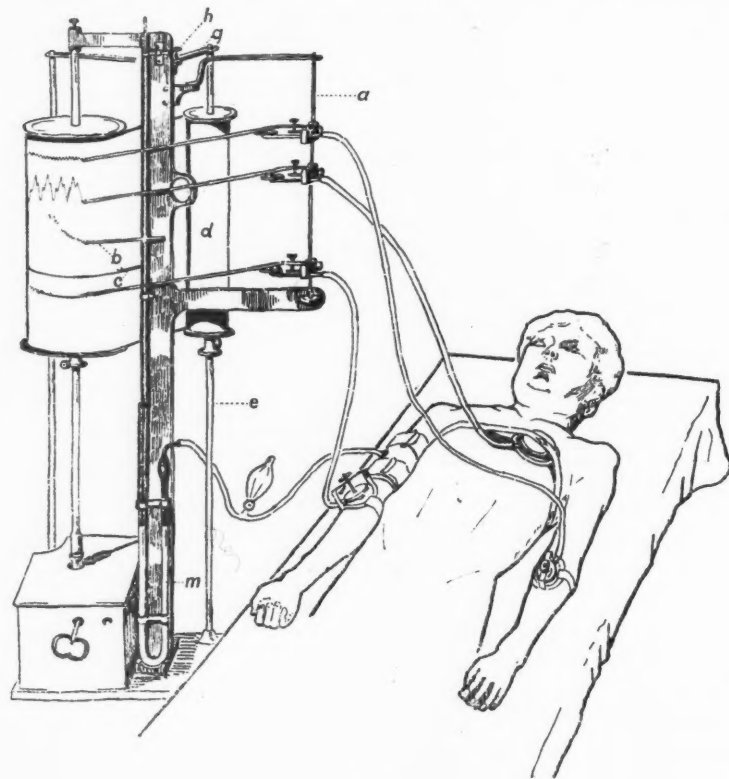
FIG. 1.

base line; it is movable up or down on the small pillar which supports it, and is kept pressed against the paper by means of a small spring.

The continuous record is obtained as follows: The recording drum is fed by a roll of prepared glazed paper 50–100 feet long, which is carried on another small drum (*d*, Figs. 1 and 2). This drum is clamped at the requisite level on an upright (*e*, Figs. 1 and 2) which revolves around a vertical axis. The paper is led off from drum *d* (Figs. 1 and 2) round the surface of the recording drum, where the various styles write upon it; and it is kept in position by means of

an adjustable spring mounted on a pillar. The paper bearing the tracing then falls away from the drum on to the table. A glance at the figures will amplify this description. The clockwork has had to be considerably strengthened to enable it to draw the paper from the feeding drum; but it has the same characters as in the original Gibson machine, viz. it attains full speed almost immediately after starting, and runs at a constant velocity. Both drums are flanged to prevent the paper slipping; and these, together with the spring, can be moved up or down their respective pillars to the required level.

The feeding drum can be removed by taking off the cross-bar (g, Figs. 1 and 2) after unscrewing the screw (h, Figs. 1 and 2). The upper end of the drum is also removable and a roll of paper can then be slipped over the cylinder.
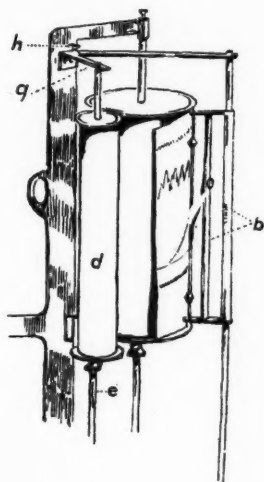
FIG. 2.

FIG. 3.

A space has been left in the middle of each roll into which this cylinder fits exactly. In using this apparatus, as with other instruments, the arm is kept at about the level of the heart, either by the side of the body as shown in Fig. 1, or stretched out at right angles to it. The armlet is inflated, and the air is then allowed to escape slowly; after the pulse has definitely returned, it is again obliterated by pumping more air into the armlet. This procedure can be repeated six times or more in a minute, so that it is possible to get a reading every ten seconds or less. All the air is allowed to escape from the armlet for a few seconds in every five to ten minutes, so that the venous circulation is not unduly interfered with. Patients—even very small children—bear the continued pressure of the armlet quite well. Older children and adults say that the pressure makes the arm feel a little swollen and occasionally causes a tingling sensation; no pain, however, is felt at the time or subsequently, and no untoward sequelae are produced.

It might be thought that the exclusion of so large a portion of the vascular area would raise the blood-pressure. This objection, which has been urged against the Riva-Rocci and all armlet methods, has been shown by Oliver to be without foundation. But it might be argued that, although this objection is baseless, so far as isolated readings were concerned, yet, if the pressure be kept up over many minutes, a rise in blood-pressure must occur. Theoretically such a rise appears highly probable, but it is quite obvious from the records we have obtained that practically no such rise does occur.

We have used armlets differing in size according to age, and have thus been enabled to get traces from subjects of two years and upwards. In constructing all these armlets we have borne in mind the essential of an efficient armlet enunciated by von Recklinghausen, viz. the width of the armlet in relation to the circumference of the arm.

The recording drum moves at a known rate, so that time intervals can be marked off on the chart after the records have been obtained. To check the rate of the drum the continuous pulse trace has at times been dispensed with, and this tambour and lever has been used as a time-marker showing intervals of twenty seconds.

The measurements are subsequently taken by means of a special ruler. In cases of difficulty the pulse return is judged by examining the tracing with a lens. The first return of the pulse gives the systolic pressure : the diastolic pressure has not been systematically observed by us, since it is of no special value from the point of view of this research. Further, frequent estimations of the systolic pressure do not allow enough air to escape from the armlet to obtain a record of the diastolic pressure.

The readings thus obtained are plotted out in a graphic manner. Each unit of the ordinate is 1 mm. of mercury, and of the abscissa is twenty seconds. The various incidents that occur during the trace are indicated along the abscissa. Some of the graphs also show the pulse-rate, and in these the units of the ordinate are taken as beats per second. Others show in addition respiratory rate and amplitude ; the former is recorded in a similar fashion to the pulse-rate, while the latter is given in millimetres as a figure which is obtained by taking the mean height of the respiratory excursions occurring in a unit of time (here twenty seconds).

II. *Lumbar Puncture.*

In order to eliminate, as far as possible, the effect on the records of pain, mental disturbance, and muscular contractions, &c., tracings were obtained from subjects in varying degrees of consciousness. Before considering the charts derived from these tracings, it may be pointed out that the skin puncture is accompanied in all cases by a rise of blood-pressure, the extent of which varies with the degree of consciousness of the subject, or with the amount of pain and disturbance caused by the manœuvre. It will be seen that a similar rise in the

blood-pressure is observed under full inhalation anaesthesia in the dog. Similarly, the puncture of the dura by the needle is shown to be followed by a still more marked rise in blood-pressure in every instance, though a reference to the pulse tracing in the first of these records shows that the resulting pain and disturbance is less pronounced (Fig. 4). The charts show this definite rise in blood-pressure on puncturing the dura during all stages between consciousness and complete
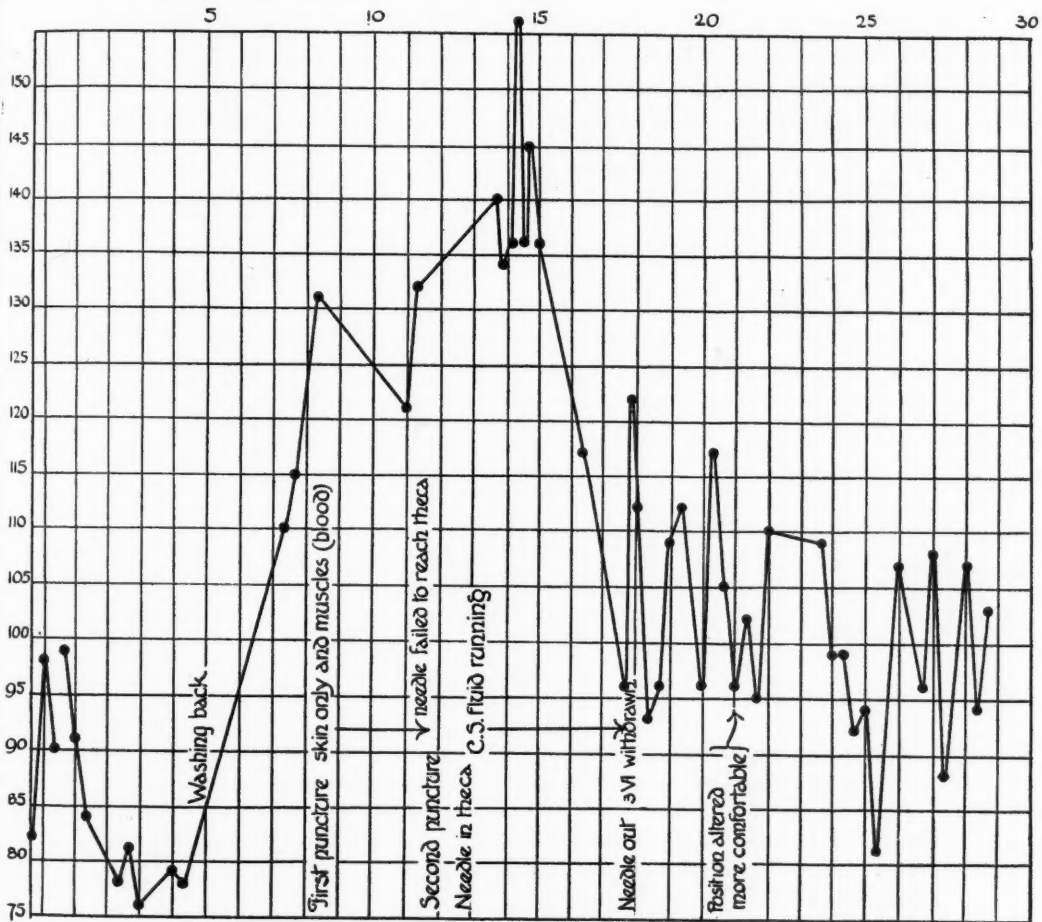
FIG. 4.   Blood-pressure record.   Ordinate in millimetres, abscissa in minutes.

unconsciousness and thus dispute the possible view that this alteration is alone due to pain or disturbance of the higher centres; they indicate that the effect is vasomotor and show that the influence on the medullary centres is definite and moderately pronounced.

The tracing of Fig. 4 was obtained from a healthy male child of seven years. This patient was said to be subject to occasional fits, and lumbar puncture was

undertaken for the purpose of bacteriological and cytological examination of the cerebro-spinal fluid. For practical purposes this record may be regarded as obtained from a human subject under physiological conditions, since tracings in the normal human subject are not obtainable. It will be seen that the blood-pressure rose, from 78 mm. Hg. to 156 mm. Hg. (a rise of 78 mm.), from the commencement of the manipulations to just after the flow of cerebro-spinal fluid. During the flow of cerebro-spinal fluid (of which six drachms were withdrawn) the blood-pressure dropped to about 95 mm., at which point the needle was removed. The tracing is continued for about eleven minutes, and during this time a very gradual continuous fall is observed in the *mean* readings. The tracing stops about *seventeen minutes* after the first flow of cerebro-spinal fluid, and at this
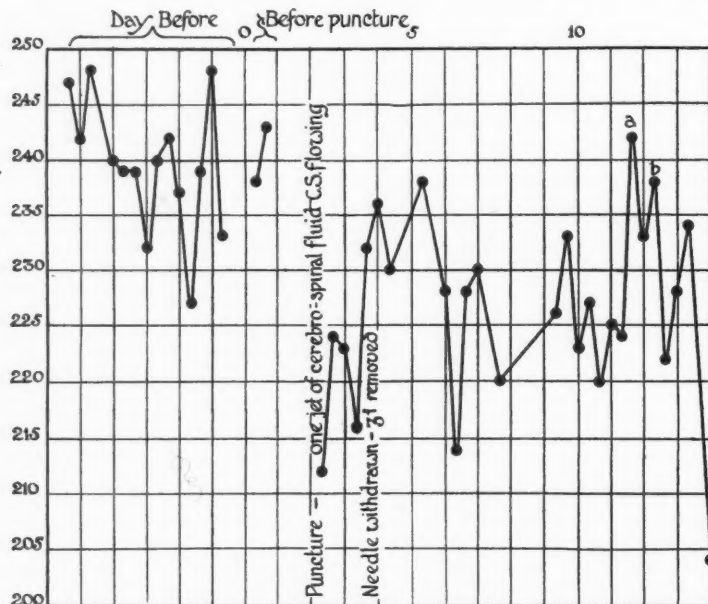
FIG. 5. Blood-pressure record. Ordinate in millimetres, abscissa in minutes.

time it will be noted that *the blood-pressure is considerably higher than at the outset.* The wide variations in the readings are due to the activity of the higher centres and the small and repeated muscular contractions of the manometer arm.

If Fig. 5 be now referred to it will appear, at first glance, that quite a different type of curve is presented; but, if examined carefully, this chart bears a close resemblance to the former, the modifications being due to the peculiar conditions of the case. In the first place the tracing was obtained from a child of $11\frac{9}{12}$ years, in the early stages of uraemia; she was the subject of marked arterio-sclerosis, and drowsiness was just commencing. On the day previous to the lumbar puncture a tracing showed that the blood-pressure varied between the remarkable figures of 248 mm. and 227 mm. Hg. Immediately before the

lumbar puncture the blood-pressure was 238–43 mm. Hg.; though, at the moment of puncture, the reading was 212 mm.: this wide variation is accounted for by the marked apprehension of the child, as well as by the constant nausea and retching. Here also a rise of blood-pressure follows the puncture. Importance cannot, of course, be attributed to the final reading, and the rise at *a* and *b*, to 242 and 238 mm. respectively, must be neglected, because the tracing shows that this rise is entirely due to the increase in respiratory amplitude and rhythm at that moment (the extent to which these factors influence the blood-pressure will be emphasized later). The respiratory tracing is not reproduced. If, therefore, we neglect the rises *a*, *b*, and the final reading, it is evident that the puncture was followed by an elevation of blood-pressure, which began to fall gradually
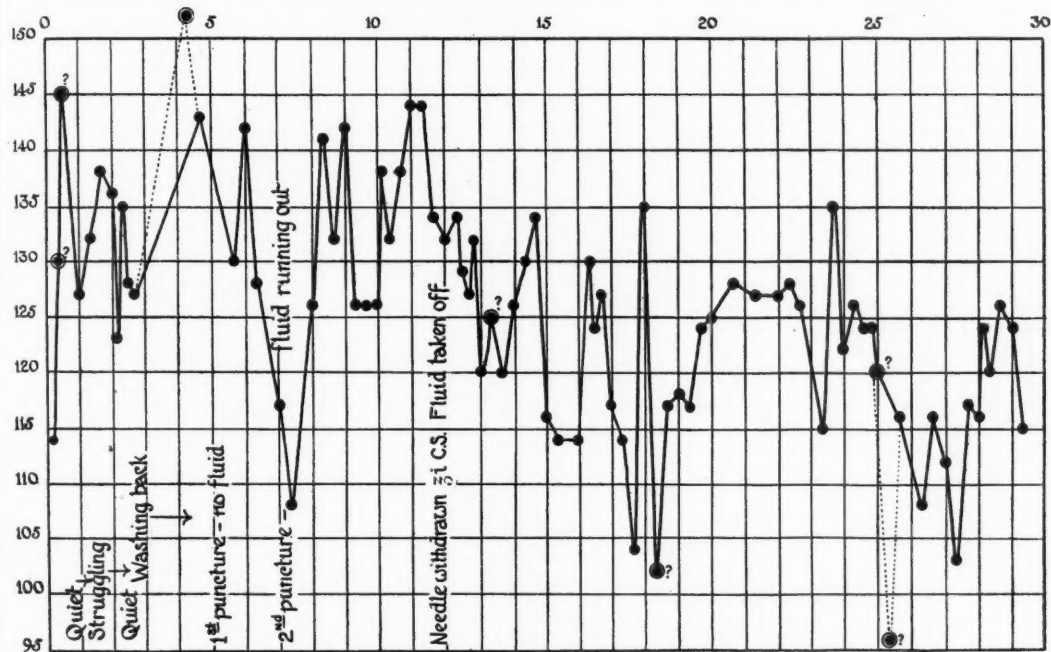
FIG. 6. Record of blood-pressure. The abscissa refers to time in minutes.

after the cerebro-spinal fluid ceased to flow. About eleven minutes after the puncture the blood-pressure had clearly reached a slightly lower level than that which followed the initial rise; though, during the time over which the record extends, the readings never returned to the original figure, but always remained above it. In this instance only *one drachm of cerebro-spinal fluid* was removed; and this fact, together with the half-drowsy condition of the patient after the preliminary manœuvres, and the enormous blood-pressure, is sufficient to account for the slight changes observed. In its general features, however, *the type of Fig.* 5 *corresponds closely with that of Fig.* 4.

Fig. 6 was taken during lumbar puncture on a child of $2\frac{3}{12}$ years, suffering

from a neoplasm of the corpora quadrigemina. Considerable patience was required to obtain a trustworthy record in so young a subject, for symptoms of cerebral irritation rendered adequate control difficult. The tracing, however, offers a few sources of fallacy. It will be seen that the chart begins at 114 mm. Hg.; and that, for five minutes, the child resented any interference to such an extent that the blood-pressure rose to between 145–123 mm. Hg.: the first (ineffectual) puncture was followed by a rise in blood-pressure, which rapidly sank to 108 mm. as the child became quieter. The figures 115–108 mm. Hg. should therefore be taken as the starting-point. The same features are recognizable in this chart as in the preceding ones, and detailed description is therefore unnecessary; but, in spite of the gradual fall in blood-pressure following the marked rise after the puncture of the dura, the original mean level is not regained *after about twenty-three minutes* from this time.
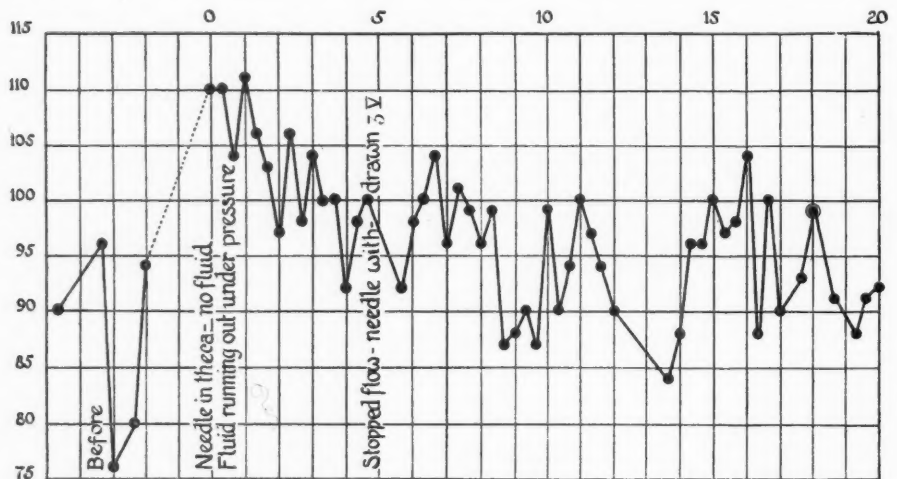
FIG. 7.   Record of blood-pressure.   The abscissa refers to minutes.

In Fig. 7, the patient, a boy of seven years, was completely unconscious, the result of a left intracerebellar tumour. The initial rise of blood-pressure was well marked; but although five drachms of cerebro-spinal fluid were withdrawn, the subsequent fall of blood-pressure was less pronounced than in any of the preceding cases, and at the end of twenty minutes was definitely higher than at the commencement of the record. The difference in this curve from the type already seen is not due to the degree of unconsciousness; this is exemplified by reference to the next chart (Fig. 8), where the intracranial pressure is even more marked, as evidenced by the additional phenomenon of 'grouped respirations'. Indeed, we submit the view that, when the increase of pressure is subtentorial in origin, the type of blood-pressure curve resulting from lumbar puncture is similar to that obtained in normal subjects, and when the pressure is supratentorial; but that all the variations of the curve are much less pronounced.

Fig. 8 was taken from a lumbar puncture in a case of a child $2\frac{1}{2}$ years, suffering from tuberculous meningitis, shortly before death—'grouped respirations' are well shown in the tracing (Fig. 9). Two drachms of fluid were withdrawn, and the marked fall in blood-pressure contrasts effectively with the slight drop in Fig. 4. Strychnine was administered hypodermically after fourteen
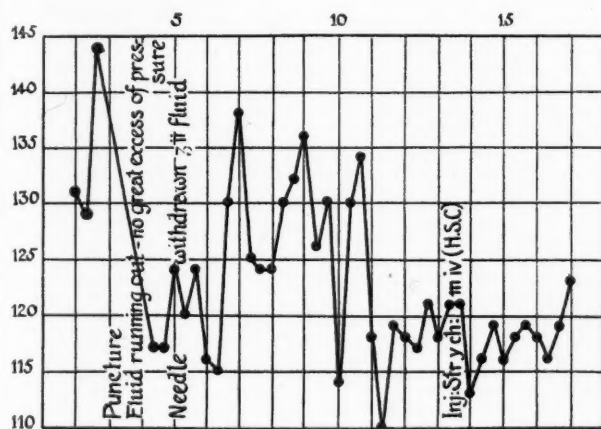
FIG. 8. Record of blood-pressure. The abscissa refers to minutes.

FIG. 9. Uppermost tracing, apex beat; second tracing, manometer record; the brachial pulse is shown below.

minutes, and the rise in blood-pressure, probably resulting therefrom, is seen to take place shortly after two minutes have elapsed. Experiments on animals support the view already advanced, viz. that the preliminary rise in blood-pressure is not entirely due to the disturbance and pain resulting from the lumbar puncture. This is confirmed by the tracing of a lumbar puncture in the dog under full chloroform anaesthesia (Fig. 10). Fig. 11 is prepared from Fig. 10 on similar lines to the charts of the tracings on the human subject, so that comparison may be easier. The rise of blood-pressure from puncturing the dura mater is seen to be greater than that following the skin puncture, and the subsequent fall not well marked. In the case of the dog, no cerebro-spinal fluid could be obtained. Finally, it appears that, although as a rule the withdrawal of cerebro-spinal fluid tends *per se* to lower the blood-pressure, the net result of lumbar
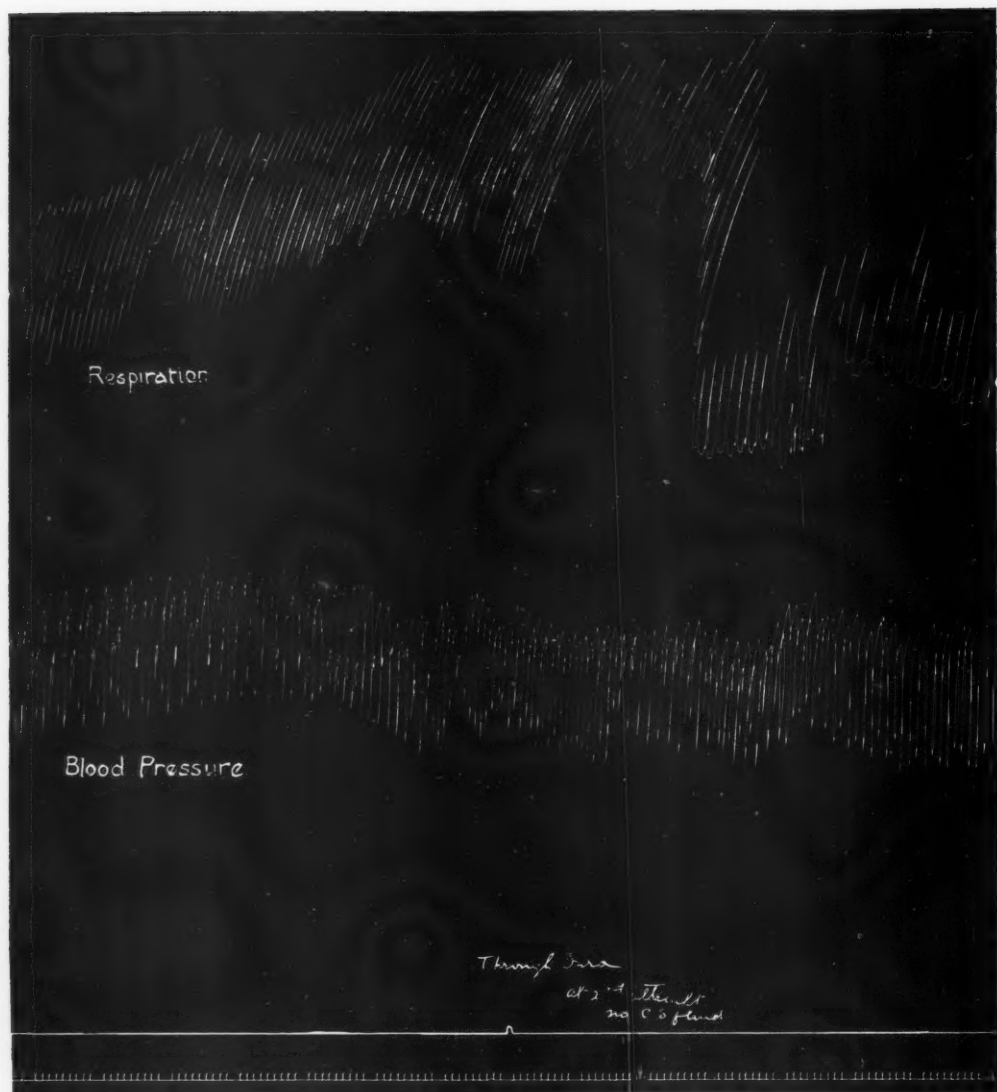
FIG. 10. Tracings of respirations and blood-pressure from a dog under anaesthesia to show the effect of puncturing the dura mater and pinching the skin. Time-marker in seconds. Towards the end of the tracing the respiratory lever was lowered.

puncture *is to raise it for at least twenty minutes afterwards*. This point is of importance in connexion with spinal anaesthesia.

III. *Spinal Anaesthesia.*

A. *High anaesthesia.* It has been stated that the blood-pressure falls in a patient who has been subjected to a spinal anaesthetic, and various reasons have been put forward to explain this phenomenon—as, for instance, that paralysis of the abdominal walls causes engorgement of the mesenteric vessels; or that paralysis of the splanchnic nerves induces dilatation of the mesenteric arteries and arterioles. These views were criticized by one of us elsewhere (2), and it was stated that, though such factors might play a small part in the phenomena observed in a certain number of cases, they were probably of secondary importance. The opinion was also expressed that, though the fall in blood-pressure might be attributable, to a small degree, to the action of stovaine on the centres (depending on the degree to which the fluid employed had been rendered *indiffusible*), in the main the extent of the fall varied directly with the extent of the paralysis of the intercostal respiratory muscles.

FIG. 11. Blood-pressure plotted from Fig. 10.

We have obtained numerous records of operations performed under spinal anaesthesia; some of these we now propose to consider in order to obtain a definite view as to the changes of blood-pressure accompanying spinal anaesthesia, and to ascertain the conditions on which these depend.

1. *Blood-pressure.* It would be a great advantage to obtain a tracing from a case submitted to spinal anaesthesia alone, and uncomplicated by any operative manipulations; this, of course, is impossible; but the nearest approach to this we could obtain is shown in Fig. 12. This chart was taken from a girl of three years, during the performance of an operation for inguinal hernia. The sac was tied before the commencement of the continuous trace, so that the subsequent readings may be taken as uninfluenced by any of the steps of the operation. It will be seen that there is a total fall in blood-pressure amounting to 35 mm. Hg., and that anaesthesia was induced up to the second dorsal segment. As the paralysis spreads over the abdomen, and while the chest is as yet unaffected (as shown by the constancy of the respiratory trace), the blood-pressure shows a steady fall of 15 mm. Hg. From the eleventh minute in the chart there is a sudden drop in the blood-pressure, which, with one intermission, continues a very slight gradual fall until just before the end, the total remaining fall amounting to 20 mm. Hg.

The causes of these changes in blood-pressure are of the highest importance
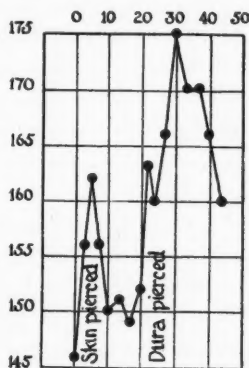
in the investigation before us, and the explanation of them is made clear from a simultaneous examination of the respiratory tracing. In the first place, it has been stated that, from the commencement of the chart as far as the eleventh minute, the blood-pressure falls 15 mm. Hg.; during this period there was no alteration in the character of the thoracic respirations, though paralysis is complete over the abdominal muscles. At the first raising of the pressure in the manometer (Fig. 13) there is indication that the paralysis is beginning to involve the intercostal muscles; for the character of the respirations begins to alter, the thoracic excursions becoming rapidly smaller and the diaphragmatic excursions becoming suddenly pronounced. For it is a matter of common clinical experience that, during spinal anaesthesia, when the paralysis reaches the fourth or fifth dorsal segment the respirations become almost entirely diaphragmatic.

The first fall of blood-pressure (15 mm.), extending to the eleventh minute, may be attributed in part to the flaccid paralysis of the muscles of the limbs and abdomen, owing to which pressure is removed from veins, capillaries, and arteries, and in consequence their calibre is increased. It cannot be maintained that there is any stagnation of venous blood in the veins under these conditions, for our clinical observation is absolutely contradictory to this view; also, gravity is a negligible factor when the subject is in the supine position.

The fall in blood-pressure, therefore, is, partly at any rate, due to the *increased capacity of the vascular system as a whole, and represents a mechanical fall in the general blood-pressure.* Other factors which influence this preliminary fall will be referred to again.

At the eleventh minute a further sudden fall in pressure occurs synchronously with a marked diminution in the thoracic excursions, and with the development of exaggerated diaphragmatic respirations. Now one of the great factors in supplying the auricles with blood, which is to be passed on to the ventricles and so into the general arterial system, is the negative pressure in the thorax. Whether this 'aspiration' acts by relieving the pericardium from pressure, thus facilitating the influx of blood to the heart chambers, as stated by Lewis to occur under anaesthesia; or whether, as we think more likely, inspiration favours, in this manner, the expansion of the great veins, and so brings more blood to the heart; our observations seem to show that the negative pressure induced by inspiration influences the maintenance and the respiratory variations of the arterial blood-pressure.

In order to understand the effects on the blood-pressure of inducing paralysis as far as the sixth dorsal segment, it is necessary to consider in brief outline some of the principal factors in the mechanism of respiration: for our observations on the human subject seem to be rather at variance with the findings of Lewis, regarding the effect of prolonged thoracic inspiration on the blood-pressure. Keith has shown that the respiratory mechanism is extremely complicated, and in this paper we can only consider some of the leading factors concerned. Thus, briefly, according to Keith, the expansion of the upper lobes of the lungs takes place in a conical form as seen in the accompanying diagram (Fig. 14), *a b c*
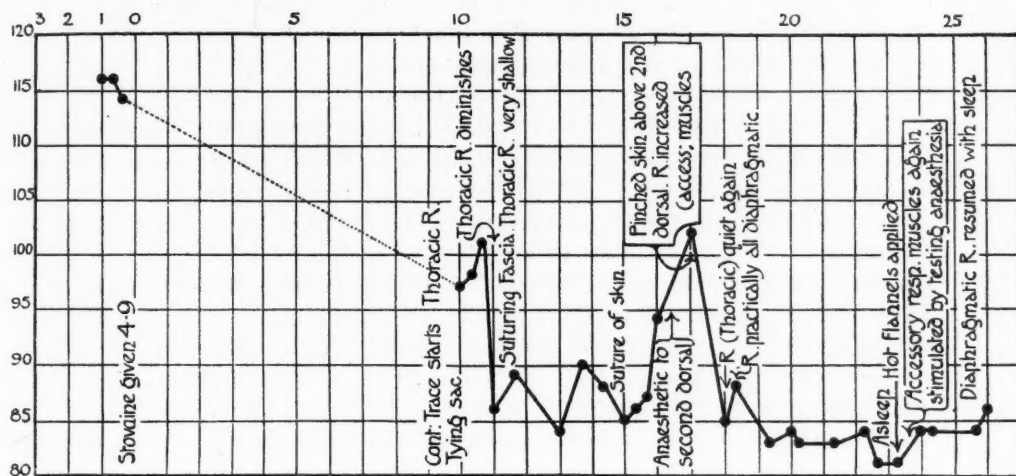
FIG. 12. Tracing of blood-pressure. Abscissa in minutes.

86   89
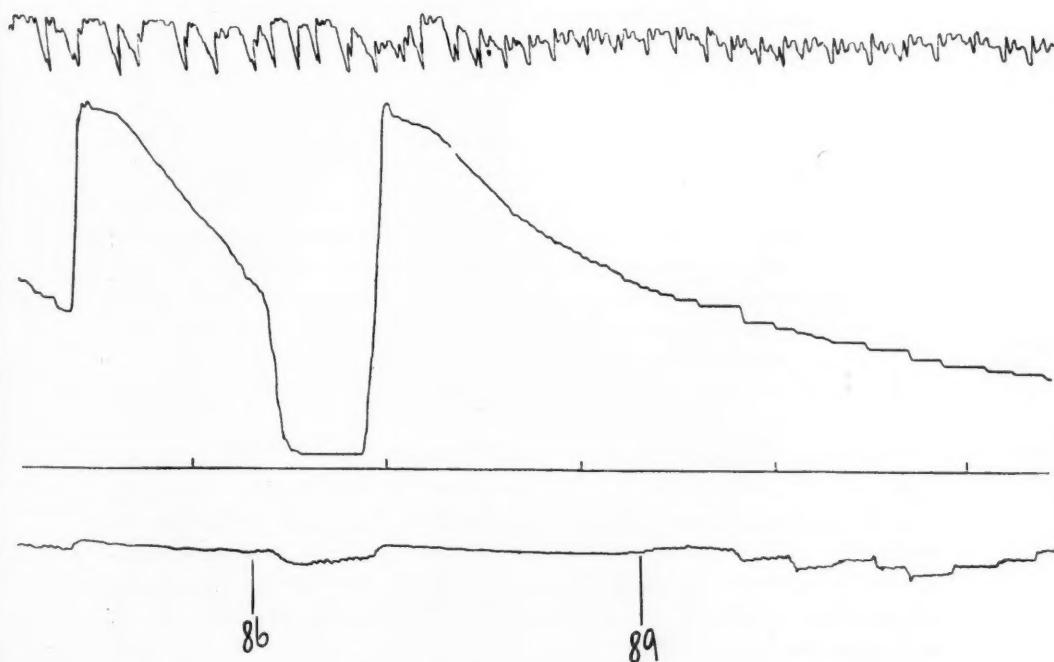
FIG. 13. Upper tracing is from the apex beat, middle from the manometer, lowest from the brachial artery.

expanding into $a\ b'\ c'$. This expansion is brought about by the movements of
(1) the first pair of ribs and the manubrium sterni (the thoracic operculum), and
(2) the second to the fifth ribs with their costal cartilages.

The lower lobes of the lungs are expanded in a cylindrical form according
to Fig. 15; thus $b\ c\ d\ e$ expands into $b'\ c'\ d'\ e'$ by the expansion of the lower
thorax and the piston-action of the diaphragm in its downward and forward
course. Without entering into detail this mechanism may be regarded as the
result of the combination of synergic and antagonistic muscles in the following
way: The elevation of the lower thorax (sixth to tenth ribs) takes place by
the antagonistic action of the supra-umbilical muscles and the downward and
forward movement of the diaphragm; thus the former, by forcing the abdominal
viscera against the diaphragm during the contraction of the latter, provide
a fulcrum which tends to expand and raise the lower thorax. Thus, in Fig. 16, the
contraction of the supra-umbilical muscles (A.M) pushes upwards the viscera,
which provide a fulcrum (F) against the downward movement of the dia-
phragm ($f\ g\ h$). The diaphragm, as a result of this, assumes a position $f'\ g'\ h'$;
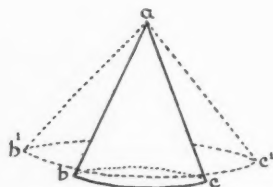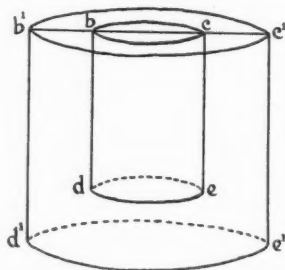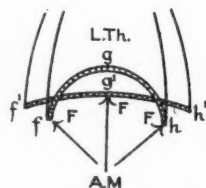
FIG. 14.   FIG. 15.   FIG. 16.

and the points $f\ h$ are raised to $f'\ h'$. Fig. 16 also shows the elongation of
the thoracic cavity by the downward movement of the diaphragm (*L. Th.*).
Further, if the visceral fulcrum be neglected, the diaphragm alone also tends, in
its contraction, to pull inwards and downwards the sixth to the tenth ribs;
and the antagonistic action of those muscles which, during inspiration, tend
to raise these ribs (providing thereby a fixed origin for the diaphragm) must
be included in this mechanism.

The combination of such a number of factors renders the respiratory act
a very complex, as well as a variable, mechanism. This mechanism, in so far as
it affects the negative intrathoracic pressure, is of importance in the present
study; but a further factor in the influence of the respiratory act on the blood-
pressure must not be neglected. Thus the pressure of the abdominal muscles on
the underlying viscera favours the flow of blood in the great veins in the line of
least resistance, i.e. towards the heart.

If we now pass on to consider the modification in the respiratory mechanism
consequent on a paralysis to at least the sixth dorsal segment (as in the case of

high spinal anaesthesia under consideration, Fig. 12), it will be apparent that the expansion of the lower thorax is diminished. For, in the first place, the paralysis of the supra-umbilical abdominal muscles removes the fulcrum (F, Fig. 16), whose opposition to the downward excursion of the diaphragm is dependent on the action of these. The chief factor, therefore, in the elevation and expansion of the lower thorax is in abeyance. Secondly, those muscles which by their combined contractions tend to raise the sixth to the tenth ribs are paralysed; that is to say, the antagonists of the inward pull of the diaphragm on the ribs are also in abeyance; so that each inspiratory contraction of the diaphragm is accompanied by marked lower thoracic recession with bulging of the abdomen. In short, the diaphragm is acting at a very great disadvantage. Thus, diagrammatically (Fig. 17), if D represents the inward pull of the diaphragm on the ribs, D will be opposed by an equal and opposite antagonist, A, which will afford D a fixed *point d'appui*. Now A is the resultant of two forces, (1) V, or the combination of muscular actions which tend to elevate the ribs; and (2) R, the resistance due to the shape of the rib. It is clear that when V is in abeyance, as in high spinal anaesthesia, R can be no antagonist to D. Clearly
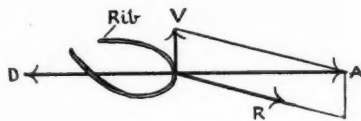
FIG. 17.

no overaction of the diaphragm could compensate the deficient expansion of the lower thorax under these conditions. Further, the paralysis of the abdominal muscles removes one of the factors favouring the return of venous blood to the thorax, since the intra-abdominal pressure is considerably diminished.

We conclude that the bulk of the fall in arterial blood-pressure during high spinal anaesthesia is attributable (1) to the diminished negative intrathoracic pressure during inspiration, consequent on the abdominal and lower thoracic paralysis (provided always that absorption of the anaesthetic agent is reduced to a minimum); (2) to the diminished pressure on the large abdominal veins during inspiration, due to the flaccidity of the abdominal muscles, and to the fact that the diaphragm is acting at a disadvantage.

There is still further evidence in favour of this conclusion. If Fig. 12 be referred to again, a marked rise of blood-pressure at the eleventh minute occurs when, during the testing of the upper limit of paralysis by pinching the skin, the area of unimpaired sensation was reached. Tracings (Figs. 18 and 19) show the respirations immediately before and after pinching the sensitive area.

Though the test showed that the paralysis reached the second dorsal segment,

and the tracings show that, up to this point, the respirations had been almost entirely diaphragmatic, nevertheless this disturbance is followed by a wide increase in the capacity of the thorax, as evidenced by the excursion of the respiratory lever and notwithstanding the paralysis of the intercostal muscles. This increase in the sagittal and coronal diameters of the thorax takes place through the agency of the *accessory respiratory muscles*, which, by their contraction, raise the thorax as a whole. As a result, force v (Fig. 17) is restored to a great extent; and, therefore, during the action of these muscles, the normal
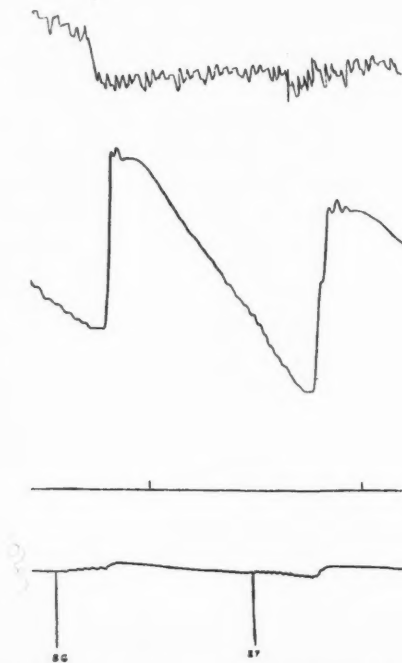
FIG. 18. Upper tracing is from the apex beat, middle tracing from the manometer, lowest from the brachial artery.

mechanism is approximately restored; the negative pressure in the thorax is therefore, increased, and the arterial blood-pressure rises.

For, whereas a deep inspiration, from overaction of the diaphragm, produces no marked rise of blood-pressure; one deep inspiration from the expansion of the chest, through the contraction of the accessory respiratory muscles, produces a very marked elevation—a fact which still further supports the view that *overaction of the diaphragm does not compensate the diminution of the negative pressure in the thorax resulting from the thoracic paralysis.* Finally, the rise of blood-pressure at the eleventh minute corresponds closely with the tracing at the same point: this fact supports the contention that, after this

point, the further fall is due to the altered character of the respirations, as shown in the respiratory trace. It must not be forgotten, moreover, that, amongst the subservient causes of the initial fall of 15 mm., the restfulness usually induced by spinal anaesthesia (amounting in some cases to sleep) also tends to lower the readings to a small degree.

2. *Blood-pressure pulse ratio.* The above conclusions are based both on the clinical observations and experimental studies of a large number of cases.
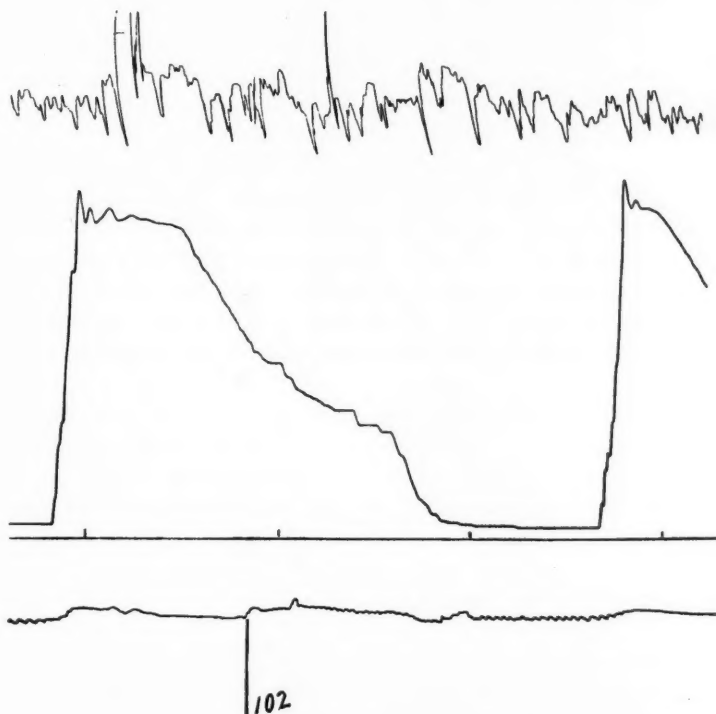
FIG. 19. Upper tracing is from the apex beat, middle tracing from the manometer, lowest from the brachial artery.

Many charts could be shown, and some will be found subsequently, illustrating the effect on the blood-pressure of thoracic paralysis, though these results are sometimes obscured by variations due to other causes.

Fig. 20 is in all respects similar to Fig. 12, and illustrates the same points, which, however, are more pronounced; at the same time we have an additional assistance in interpreting the meaning of the variations if the pulse-rate is charted simultaneously. Fig. 20 shows the pulse-rate synchronously with the blood-pressure: to obtain this record, the pulse trace is marked off into

divisions of twenty seconds, which corresponds closely with the times at which the blood-pressure readings are taken, and the results are converted into beats per minute.

Since the pulse-rate represents fairly accurately the state of mind of the child, and therefore any amount of disturbance created by any given manœuvre, it is an efficient additional control in the correct interpretation of the blood-pressure changes. The chart shows that another factor is partly responsible also for the original drop in blood-pressure, referred to in the study of Fig. 3— namely, *the subsidence of the disturbance caused by lumbar puncture* (1); for both pulse and blood-pressure readings, immediately after the puncture, show a marked fall.

Further, we have noted in the majority of the charts that, before operation commences, the original reading is higher than the repeated controls. We conclude therefore that the subsidence of mental activity (in the form of anxiety, curiosity, &c.) is also a factor in this preliminary fall; and that, in most cases, the blood-pressure at the outset is abnormally high. The influence of all these subsidiary factors in the preliminary fall of pressure accompanying a high spinal anaesthesia reduces the supposed importance of abdominal venous engorgement to a minimum; and we may conclude that such a factor plays no part of any importance—indeed, that it does not exist to any degree in the supine position.

Finally, attention must be called to the rise in the pulse-rate, accompanying the stimulation of the skin above the paralysed area; this shows that the simultaneous rise in blood-pressure is not connected with any of the steps of the operation : for in this and in other charts it will be evident that, apart from such 'independent' causes, *the pulse does not closely follow the blood-pressure in its variations during spinal anaesthesia* ; but that a certain degree of resemblance is often seen owing to the consciousness of the subject.

3. *Blood-pressure respiration ratio.* The important influence exerted by the thoracic excursions on the blood-pressure in high spinal anaesthesia has been referred to ; and in order to illustrate this further, as well as to interpret correctly any variations observed in the blood-pressure tracing, we also record on the chart the respiratory amplitude and rate. The respiratory tracing is marked off into intervals of twenty seconds; the number of respirations is then counted in each division and converted into respirations per minute. The respiratory amplitude (thoracic) is estimated by measuring the height of the inspirations, taking the average height in millimeters in each division. The results thus obtained are charted synchronously with the blood-pressure readings.

Fig. 21 is taken from a case of tendon transplantation in a girl $4\frac{2}{12}$ years under high spinal anaesthesia. Here again, the type of blood-pressure chart is in all respects similar to the two previous ones, with the exception that toward the end of the operation the anaesthetic is beginning to wear off, as evidenced
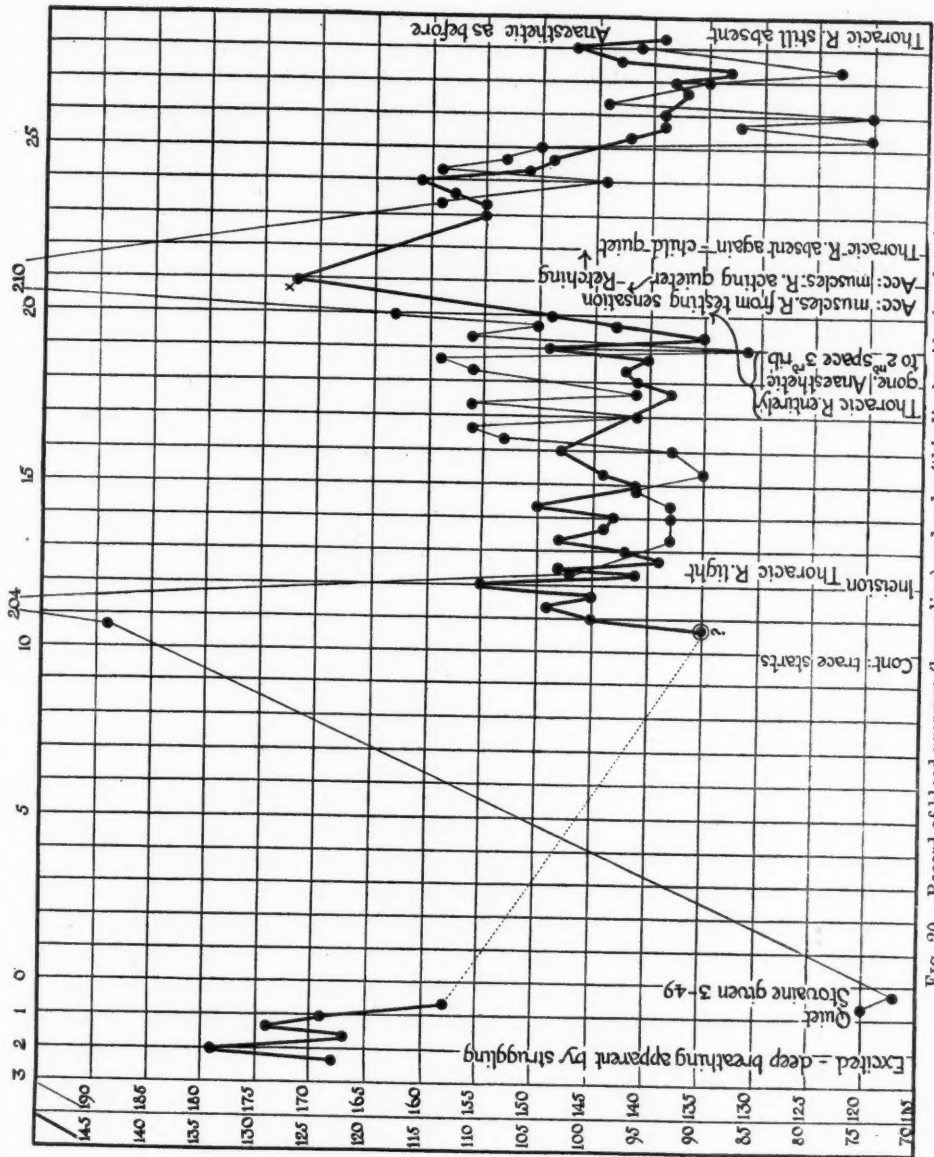
Fig. 20. Record of blood-pressure (heavy line) and pulse (thin line). Abscissæ in minutes.

by the rise in blood-pressure due to the return of thoracic respiration. Both respiratory rate and amplitude are shown in the chart, and the relation of these to the blood-pressure must claim a moment's attention. With regard to the respiratory rate, it is clear that, allowing for experimental error and excluding the fall at X, there is hardly any variation throughout; and that such variations as are seen bear no relationship to the alterations of blood-pressure. Again, turning to the amplitude of the respirations, it is noticeable that, generally, the type of curve presented by these follows closely that of the blood-pressure.

The most striking feature of Fig. 20, however, is the marked alteration of all the chart lines at X when the patient became restless for a few moments. The excursion of the blood-pressure is really much higher than shown in the chart, because for three minutes no readings could be taken: this rise is clearly caused by the action of the accessory respiratory muscles (see Figs. 12 and 20), and it is clear that with the increase in the *amplitude* there is a correspondingly marked fall in the *number* of respirations.

Now it is a matter of clinical knowledge that one deep voluntary inspiration will occupy a time equal to several smaller involuntary acts; consequently, where such inspirations occur, the respiratory rate will fall. In these charts, therefore, when the rate and amplitude lines move in *opposite* directions (as at X, Fig. 21), it is an indication that the *respirations are voluntary and increased by the action of the accessory respiratory muscles*. This chart (Fig. 21) is reproduced to demonstrate for the purpose of this paper, what is quite evident from a study of the complete tracings, namely, that it is the *voluntary inspirations, by means of the accessory respiratory muscles*, and, to a lesser extent, the activity of the higher centres, which are together responsible for the marked deviations from the common type of blood-pressure chart during spinal anaesthesia. It is essential, therefore, to eliminate these variations in order to determine the type of chart resulting from any *particular spinal anaesthetic*.

Finally, it is interesting to observe how closely the gradual rise of blood-pressure, towards the end of the operation, is accompanied by a rise in the amplitude of respirations; this shows that the blood-pressure, at this point, is rising with the return of thoracic respirations, and again emphasizes the importance of the diminution of thoracic respiration as a cause of the fall in blood-pressure.

Before leaving the question of high spinal anaesthesia it is necessary to refer briefly to the mental influence on the blood-pressure. It is evident that the consciousness of the subject introduces such an element of fallacy into the interpretation of charts that it is impossible to be too careful in avoiding mistakes; and, if such causes of inaccuracy be carefully excluded, we shall find that all of these charts follow the same type.

The effect of the emotions on the blood-pressure has been investigated by us, and we have found that the activity of the higher centres produces a marked elevation of the blood-pressure, as well as an increase in the range

Fig. 21. Record of blood-pressure (thick line), amplitude of respirations (average in 20 sec.) (chain line), and number of respirations per minute (broken line). Abscissa in minutes.

o c 2
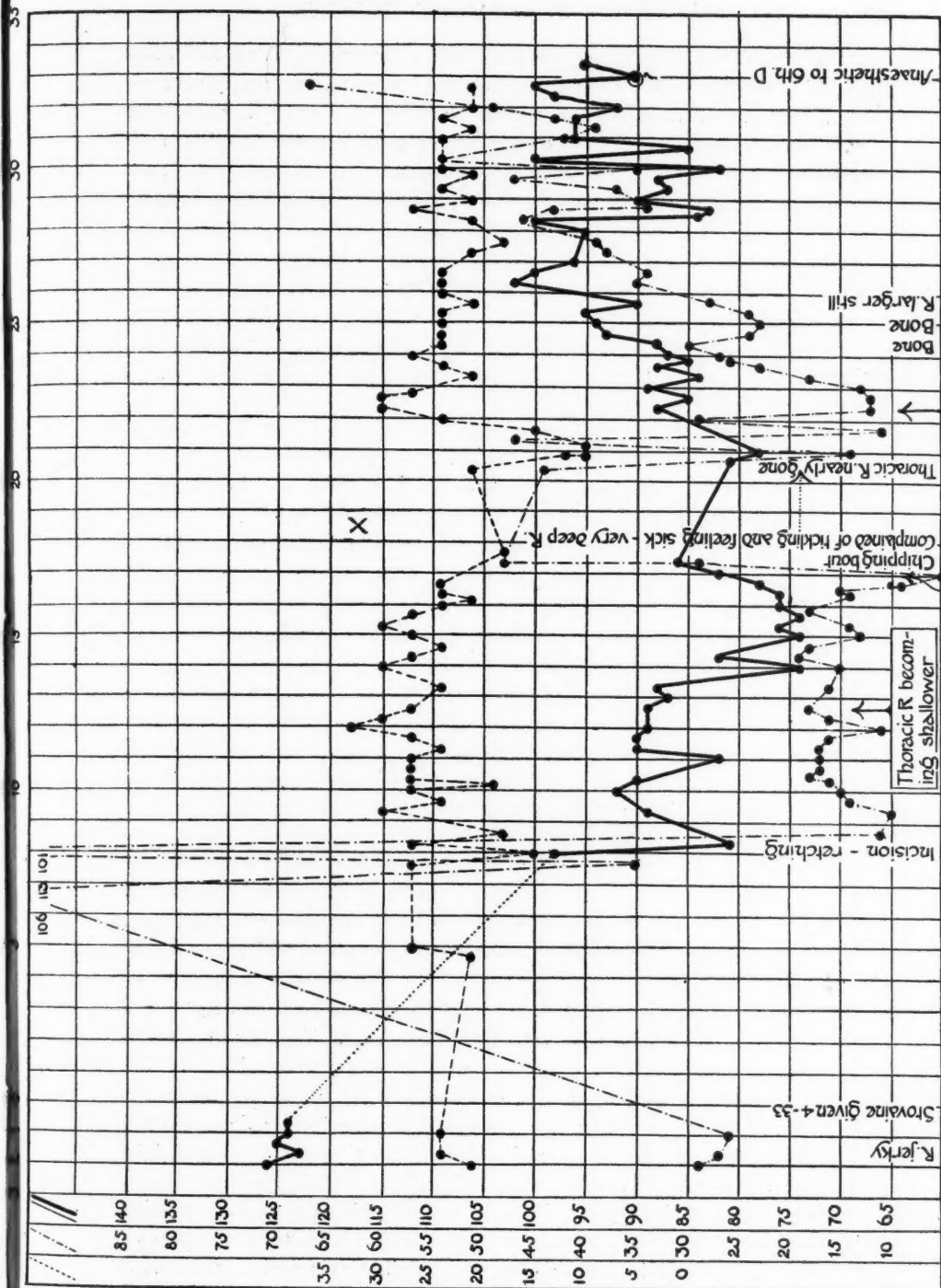
of variations. The study of the preceding charts and tracings has made it clear that, with the activity of the higher centres, the pulse and respiratory rhythms are accelerated, and, most important, that voluntary inspiration is called into play. The extent of these changes clearly takes place in direct proportion to the degree of excitation of these centres. It has been shown that indication of such disturbance is to be seen in the respiratory tracing; a fact which becomes increasingly evident as more charts are studied.

Now, the conclusions which have been already arrived at must be applied in a consideration of the effect of the mental element on the blood-pressure in spinal anaesthesia. To do this accurately, it is necessary to include records of pulse-rate, respiratory rate, respiratory amplitude, and blood-pressure in the same chart. The extent to which this factor can affect the tracings may be seen by comparing Figs. 22 and 23.

The charts are taken from boys of $6\frac{1}{2}$ and 10 years respectively, during the performance of operation for the radical cure of inguinal hernia and undescended testis. In each case a fairly high anaesthesia, involving the lower part of the thorax only, was administered. In the case of Fig. 21, the boy was singularly phlegmatic and quiet; in fact, the tracing of this case presents one of the most regular and uninterrupted types we have been able to obtain on a child during consciousness. The boy very soon became quiet after the preliminary disturbance of the lumbar puncture and injection, and the marked regularity of all the trace lines after this point is a notable feature.

It will be noted that the upper respiratory trace line remains at a practically constant level, while the amplitude line (lower) rises throughout to a slight degree, the blood-pressure line following the lower one. The regularity of the pulse line also should be noted, for the variations above and below the mean level are about equal; with regard to these variations, it must be remembered that the pulse-beats are counted within arbitrary intervals, and the figure obtained is arithmetically converted into beats per minute. Individual variations in the pulse-rate, therefore, are to be neglected, and only the general direction of the mean curve relied on, since the liability to experimental error is very great. A detailed description of the chart is unnecessary, as, on careful examination, the readings explain themselves.

As a contrast to the mental placidity, so pronounced in Fig. 22, let us examine Fig. 23, taken from a nervous boy of 10 years. The same operation was performed under the same conditions, and lasted very little longer. The first feature which is obvious in this chart is that, *as a type*, the record is exactly similar to the preceding one. In detail it is noticeable that, after the lumbar puncture and injection, the blood-pressure rises to a great height (150 mm.); the reason for this is well explained by a simultaneous reading of the pulse-rate and respiratory amplitude, in both of which the marked rise not only causes the higher blood-pressure reading, but also indicates the degree of mental disturbance. It is further clear that, during this period, there is a marked irregularity of the respiratory rate which contrasts with the regularity

FIG. 22. Record of blood-pressure (thick line), pulse (thin line), amplitude of respirations (average in 20 sec.) (chain line), and number of respirations per minute (broken line). Abscissa in minutes.

as the child becomes quieter towards the end of the operation. A very good example of the influence of voluntary inspiration on the blood-pressure is seen at X; and the latter half of the chart is particularly valuable in illustrating the effect of recovery from the paralysis. Thus, at this period the patient is quite quiet (with the exception of the rise at X, already referred to); the respiratory and pulse rates both remain practically constant; while, with the return of sensation from above downwards, the amplitude of the thoracic excursions shows a steady rise, and *is closely accompanied* by a similar steady rise in the blood-pressure.

Attention is once more called to the fact that, when sensation has returned as far as the lower abdomen at the conclusion of the operation, the blood-pressure finally reaches a point (126 mm.) equal to the original readings before puncture—a fact which still further confirms the assertion that the rise of about 25 mm. Hg., following lumbar puncture, was mental in causation, and exceeded the normal in this case by at least that figure. A detailed examination of this chart illustrates many of the points already referred to in connexion with previous charts.

Finally, reference must be made to the occurrence of vomiting and retching. Fig. 24 represents a tracing taken from a girl of six years, to whom a spinal anaesthetic was administered for operation on a tuberculous abscess of the leg.

Now it has been elsewhere shown by one of us (loc. cit.) that the rate of spread of the paralysis upwards varies, in postural methods, with the height to which the pelvis is raised as well as with the bulk of solution employed. In the case under consideration $\frac{4}{5}$ c.c. dextrin-stovaine was employed (a small dose for a child of six years), and, since anaesthesia for the leg only was required, the pelvis was only raised a little, and no effort was made to obtain an immediate high paralysis. Anaesthesia *slowly* reached the *sixth dorsal segment*. Though the usual changes are not so immediately apparent, yet on closer examination the chart is found to follow, as far as the point X, those already studied.

It will be seen that after the preliminary rise following the lumbar puncture all the lines return to their original levels, at which they continue up to the point X (the paralysis not yet having reached the dorsal segments, as evidenced by the amplitude line). Following this line we arrive at the point A when the respiratory line discontinues, though the original tracing shows that, for a little way further, the amplitude falls from 8 mm. (A) almost to zero. The accompanying blood-pressure line shows a rapid fall, and the child at this time began to yawn, a process which naturally tends to increase the amplitude and diminish the rate of respiration; accordingly the next reading shows the two latter lines moving very obviously in opposite directions. Vomiting subsequently occurred, and we think the chart shows that this phenomenon, following as it does the onset of paralysis of the thorax, is attributable to the anaemia of the medulla, resulting from the altered respirations and lowered blood-pressure.

The blood-pressure line rises during and before the act of vomiting, through the action of the accessory respiratory muscles, and does not fall subsequently;
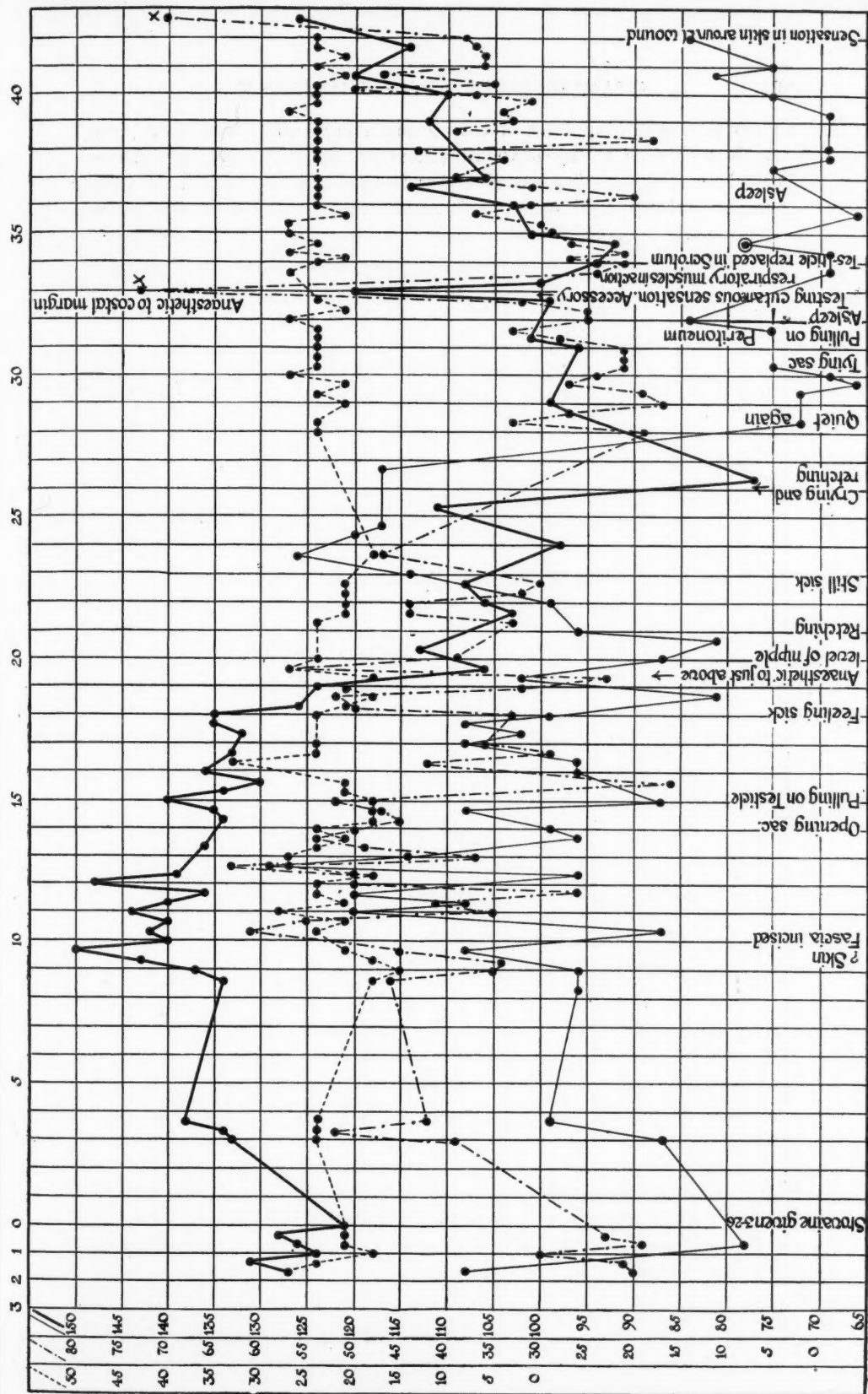
FIG. 23. Record of blood-pressure (thick line), pulse (thin line), amplitude of respirations (average in 20 sec.) (chain line), and number of respirations per minute (broken line). Abscissa in minutes.

and by this mechanism the medullary anaemia seems to be abolished. This chart is an extreme instance of vomiting from this cause ; and it is particularly instructive, since, poisoning from absorption being eliminated on clinical grounds, it shows that the paralysis of the whole thorax is not essential for the occurrence
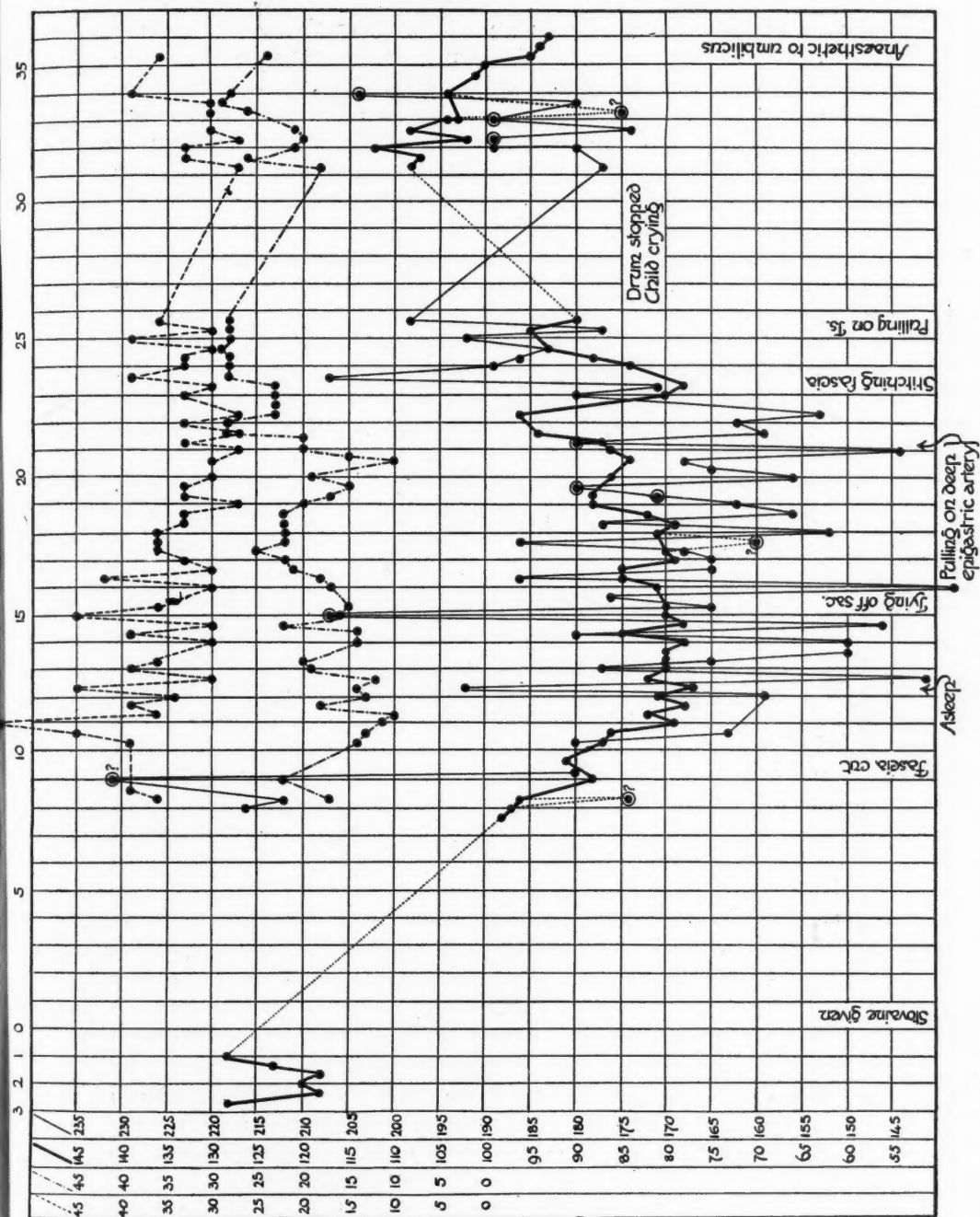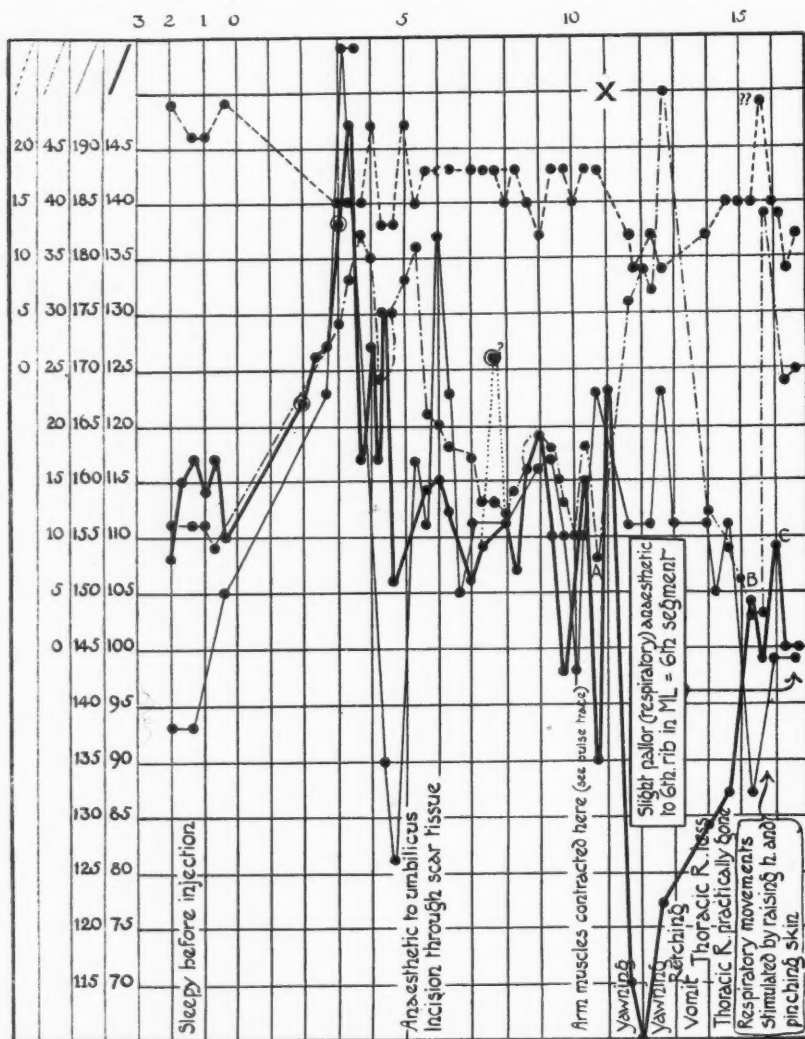

FIG. 24. Record of blood-pressure (thick line), pulse (thin line), amplitude of respirations (average in 20 sec.) (chain line), and number of respirations per minute (broken line). Abscissa in minutes.

of this phenomenon. In this case the lower six intercostals were paralysed (probably some degree of paralysis reached a little above this point) ; vomiting nevertheless ensued—a practical point worth remembering in serious cases. Anaemia of the medulla is, however, not the only cause of vomiting.

In a certain proportion of cases vomiting precedes pallor, and though the thoracic paralysis causes a fall in the blood-pressure, this is neither extreme nor announced by yawning or other signs of cerebral anaemia. To this class belong those cases where high anaesthesia is rapidly induced, and where the diaphragm quickly attempts to compensate for the rapid thoracic inactivity by overacting, and the pressure thus exerted on the stomach, which is frequently distended, induces retching or vomiting.
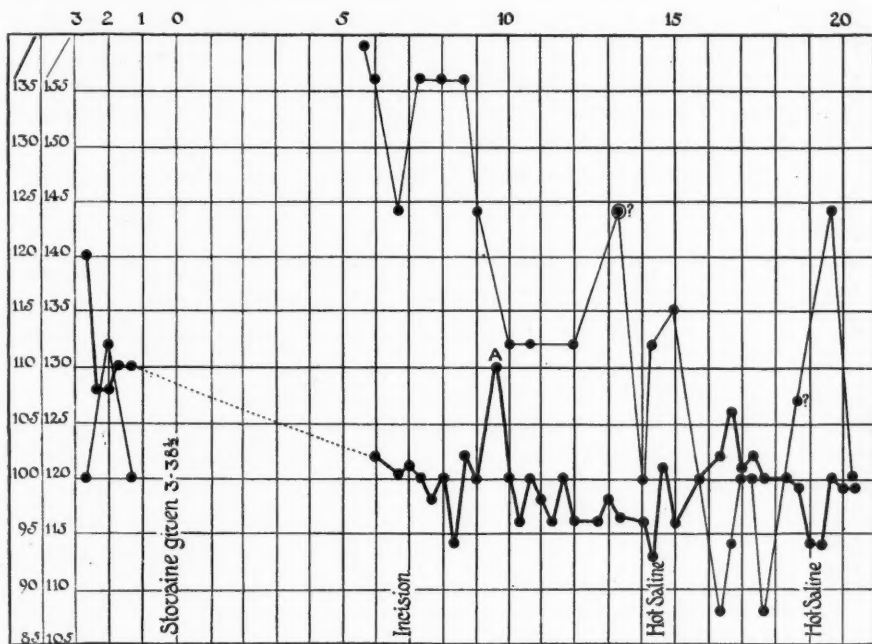
FIG. 25. Record of blood-pressure (thick line) and pulse (thin line). Abscissa in minutes.

Vomiting, therefore, occurs primarily from intercostal paralysis, inducing either anaemia of the medulla or interference with the stomach; and, in either case, it may result from paralysis to the sixth dorsal segment only.

B. *Low spinal anaesthesia.* As a final proof of the view that thoracic paralysis is responsible for the main fall in blood-pressure in high spinal anaesthesia, Fig. 25 may be now contrasted with those of the preceding section. Fig. 25 was taken from a boy of $4\frac{1}{2}$ years, who was submitted to a low spinal anaesthesia for circumcision; the respiratory trace shows that the paralysis never reached the thorax, and the whole record shows that the patient was of a quiet and placid disposition. The usual features are apparent before and after injection, namely, the abnormally high reading at the start attributable to nervous apprehension, and the subsequent fall in blood-pressure. With the exception of the small rise in blood-pressure at A, which is respiratory in origin,

the chart exhibits a perfect constancy; there is no appreciable mean fall, and the individual variations are negligible.

The contrast of Fig. 25 with those previously studied is strong evidence in favour of the views already expressed.

IV. *Conclusions.*

1. In lumbar puncture the puncture of the skin is accompanied by a rise in blood-pressure which varies in extent with the degree of consciousness, the pain, and the disturbance produced by the operation, but which is not accounted for entirely by these factors. Puncture of the dura causes a much larger rise, which is due, not to pain or the disturbance produced, but to a definite effect on the vasomotor centre. Similar rises occur in dogs under full anaesthesia.

2. Withdrawal of cerebro-spinal fluid tends *per se* to lower the blood-pressure, but the net result of lumbar puncture is to raise it for at least twenty minutes afterwards.

3. The type of blood-pressure chart obtained in lumbar puncture, when the increased intracranial pressure is of subtentorial origin, is the same as that obtained in normal individuals; or as that obtained when the increased pressure is of supratentorial origin, but in the subtentorial types the variations are less pronounced. In subtentorial cases the rise is more sustained.

4. Blood-pressure records from cases of high spinal anaesthesia show at the outset an abnormally high blood-pressure, due to mental anxiety; then a rise following lumbar puncture; next a 'preliminary fall', followed by a further more marked 'main fall' as the paralysis affects the thorax. Finally, as the paralysis passes off, the blood-pressure rises to its original value. The 'preliminary fall' is due to—

    (*a*) Flaccid paralysis of the abdominal and skeletal muscles.

    (*b*) Subsidence of the disturbance caused by lumbar puncture.

    (*c*) Onset of mental calm, amounting possibly to sleep.

The 'main fall' is due to the thoracic paralysis, which is not compensated for by overaction of the diaphragm, and consequently the aspiration action of the thorax is diminished.

5. Marked deviations from this common type of chart are due to—

    (*a*) Voluntary inspirations by the accessory respiratory muscles,

and   (*b*) to a lesser extent by the activity of the higher centres.

6. Variations in the pulse-rate do not closely follow those of the blood-pressure, but a certain degree of resemblance is often seen owing to the consciousness of the patient.

7. Vomiting during spinal anaesthesia is due to thoracic paralysis, which induces either—

    (*a*) Anaemia of the medulla,

or   (*b*) excessive action of the diaphragm, which interferes with the stomach.

8. Blood-pressure records from cases of low spinal anaesthesia show the

'preliminary fall' but not the 'main fall'. The 'preliminary fall' in these cases is due to—

    (a) Subsidence of the disturbance caused by lumbar puncture.

    (b) Onset of mental calm.

    (c) In some cases from the degree of flaccidity of the abdominal muscles.

    9. In the supine position there is no stagnation of blood in the great vessels, even when a very high spinal anaesthesia is induced.

We wish to express our gratitude to the members of the medical and surgical staff at Great Ormond Street for the material they have so kindly placed at our disposal; and also to Dr. Wm. Jeffries and Dr. L. L. C. Reynolds for their frequent assistance in taking observations.

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OEDEMA OF THE ORBITAL TISSUES

By JOHN HILL ABRAM

With Plate 18

CASES in which oedema of the cellular tissue of the orbit produces protrusion of the eyeball are in my experience very uncommon. I remember seeing a case under Sir William Gowers in 1888 in which the oedema was secondary to a naso-pharyngeal growth, with no doubt thrombosis in the cavernous sinuses. In my own practice I have met with two cases.

On March 2, 1906, Edward K., aged 30, a labourer, was admitted into my ward complaining of sore throat and pain in the right side. He had been a heavy drinker and smoker. He gave a history of pain in the side for seven weeks, some swelling in the right side of the neck, and increasing deafness.

He was dull and heavy. The temperature 104°, with the usual general symptoms accompanying such a condition. The eyelids on the right side were swollen, the conjunctiva injected and oedematous, and the eyeball obviously protruding. The naso-pharynx was coated with muco-pus.

On March 4 and 6, two and four days respectively after admission, violent epistaxis occurred. He died on March 7.

The important points in the post-mortem report may be given: 'No thrombi in cavernous sinuses. Pituitary body yellow and necrotic. The dura mater is readily stripped off sella turcica and the subjacent bone is injected and friable. The lymphatic glands in the right side of neck are twice the usual size, and the connective tissue is very oedematous. The naso-pharyngeal mucous membrane is injected. No growth found.'

In the absence of any further details I can only suggest a virulent infection of the pharynx, leading rapidly to cellulitis of the neck on the one hand, and infection of the sphenoid body and the connective tissue of the orbit on the other. The second case came under notice in February, 1910, sent to the Royal Infirmary, Liverpool, by Dr. Sugden.

The patient, Stephen D., aged 53, was an engineman in the employ of the Lancashire and Yorkshire Railway Company. He stated that eleven days before admission he was seized with violent pain in the right temple. After bearing it for three days he consulted Dr. Sugden, who ordered a blister to be applied and gave medicine. No relief was afforded. On Feb. 10 the right eye became swollen, and on the 11th he came to the hospital. He was a strong, healthy-looking man and had had no serious illness. He complained of pain shooting from right eye to vertex, which was always made worse on lying down. His temperature oscillated between 100·6° and 103·8°. His respirations were 32 and his pulse 80. My colleagues Mr. Bickerton and Dr. Hunt could find no special trouble, and the only objective signs were suffusion of the eyelids on both sides and chemosis in right eye, which was prominent. A polynuclear leucocytosis of 21,800 was present. Mr. Bickerton incised the tissues of the right orbit, but only blood escaped.

After a few days chemosis appeared in the left eye, and a little later death took place from sepsis and exhaustion.

The important points in the post-mortem report are as follows: 'Brain oedematous, normal on section. There was a thin deposit of fibrin at the base of the skull, stretching downwards from the sella turcica along the basi-occipital to the foramen magnum. The periosteum had been stripped off the sella turcica and the adjacent parts in the region of the cavernous sinuses, and these parts were bathed with yellow pus. The cavernous sinuses could not be recognized. The carotid arteries and jugular veins were normal.

Microscopical sections through the back of both orbits showed suppurative thrombosis of the orbital and ophthalmic veins; some actinomyces was present. Cultures were negative, no organisms were grown—which suggests the infection to be a pure one.

Two small pyaemic abscesses were seen in the lungs. The heart weighed 14 oz., liver 4 lb., kidneys 7 oz.; all showed cloudy swelling.'

In view of the anatomical relations of the orbital cavity to the various sinuses, nasal and maxillary, and to the zygomatic fossa, it seems curious that cases of inflammatory oedema of the orbital tissues should be so uncommon.

Blandin has examined two bodies in which a direct connexion existed between the veins of the zygomatic fossa and the ophthalmic vein at the pterygo-maxillary fissure, thus establishing a communication between the extra- and intra-cranial venous circulations; this is probably the explanation of the orbital cellulitis in my first case. My second case presents many interesting points, but I will deal with two only.

First, the diagnosis of thrombosis of the cavernous sinus; the symptoms are dependent, as Macewen points out, first upon venous obstruction, secondly upon pressure on the ocular nerves. Due to the first cause are exophthalmos, oedema of the eyelids and side of the nose, and chemosis; to the second, ptosis, strabismus, and pupillary manifestations. When these symptoms show themselves first in one eye, and the other eye becomes implicated later, the diagnosis becomes certain. 'This sequence is not constant, but when it does occur it indicates that the symptoms are due to thrombosis of the cavernous sinus and not merely to intra-orbital inflammation.' High temperatures, rigors, and vomiting, all are present also in inflammatory cases.

The reverse path may be taken to that I have suggested in my first case, and septic thrombosis in the cavernous sinus and orbit lead to infection of the pterygoid plexus and consequent oedema of the pharyngeal tissues and neck.

The second point I wish to consider is the nature of the affection—actino-mycosis. Curiously enough, almost at the time my case was under observation, Dr. Edgar Stevenson and Mr. Adair-Dighton had a case of meningitis due to actinomycotic infection, probably resulting from disease of the sphenoidal sinus. Most of what I have to say is based upon an important paper by Harbitz and Gröndahl on 'Actinomycosis in Norway', dealing with eighty-seven cases. No case of brain actinomycosis is given, except a doubtful one secondary to a primary abdominal lesion.

Osler mentions three cases, one only, Bollinger's, primary in the brain; the

other two were associated with empyema, interesting in view of the not unfrequent relationship between chronic suppuration in the chest and brain abscess. Maurice Letulle also reports a case of actinomycotic abscess of the brain secondary to pulmonary actinomycosis. The path of actinomycotic infection may be through the mucous membrane of the mouth (perhaps also the teeth), that of the intestinal canal and the respiratory tract, and occasionally through the skin. But whence? through what agent?

Hime, in an abstract of Israel's paper, says, 'it would appear then that man and animals must be infected from some third and common source.' Infection from animals has been abandoned by every one, for, as in my case, many patients have had no close association with animals subject to the disease. Of infection from man to man again we have no knowledge. In most cases we have assumed that infection comes from the external world, and sometimes, though but rarely, is associated with the presence of a foreign body—straw, splinters of wood, and so on.

J. H. Wright has suggested that the fungus leads a saprophytic life on the mucous surfaces to penetrate only with a traumatic lesion, and Lord states he had found actinomyces in carious teeth in healthy individuals. Finally I give some of Harbitz and Gröndahl's conclusions which seem most important.

1. The fungus in man is anaerobic. This may explain many failures to cultivate organism in human cases.

2. Actinomyces in nature (hay, straw, &c.) is aerobic, so far as at present determined.

3. No conclusive evidence for direct infection

    (a) from man,

    (b) from cattle.

4. Wright's view given above they cannot accept as proved.

5. Serum diagnosis and a specific serum treatment have not yet been established.

I must add that I am indebted to Dr. Ernest Glynn for the microscopic sections, photographs of which I show in Figs. 1 and 2.

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DESCRIPTION OF FIGURES.

FIG. 1. An ophthalmic vein with suppurative phlebitis with a rectus muscle above it. × 25. (E. E. Glynn.)

FIG. 2. Mass of actinomyces surrounded by pus cells from vein in Fig. 1. × 200. (E. E. Glynn.)
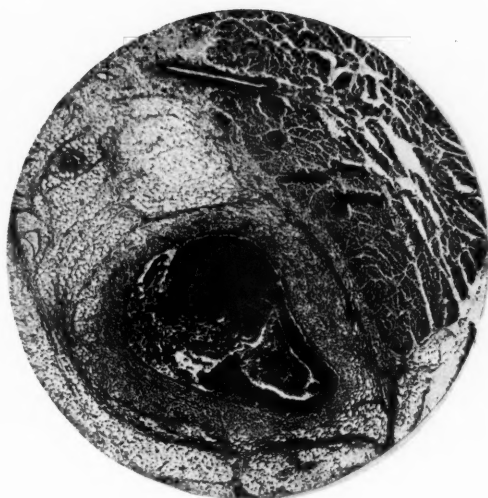
Fig. 1
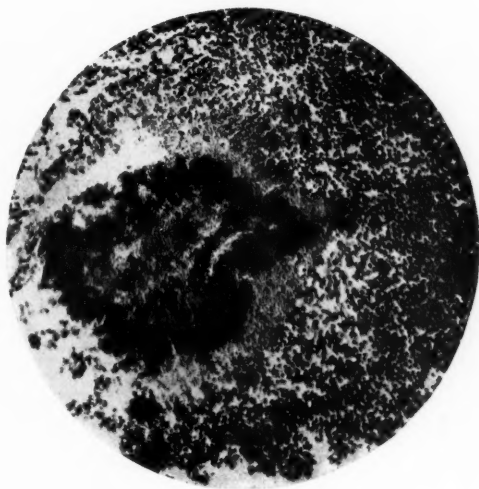
Fig. 2

REMARKS ON SYPHILITIC PSEUDO-TABES, WITH THE RECORD OF A CASE

By W. B. WARRINGTON

J. P., aged 42, admitted to hospital Dec. 9, 1910. The patient acquired syphilis eight years ago. A few years later he noticed a loss of balance in walking, and about the same time an unsteadiness in using his hands, so that he found it difficult to write. For some time he had suffered from severe pains in the head and legs. More recently loss of control over the bladder had set in.

He was a poorly-nourished anaemic man of good intelligence. His gait was very ataxic and Romberg's sign marked. The arms could not be held out steadily in the horizontal plane, the whole upper limb trembling; he was, however, able to pick up and touch objects with fair precision, and without exhibiting the typical incoordinative movements.

Although the general wasting was marked, there was no localized atrophy. The lower limbs were slightly hypotonic. There was no paralysis of limbs or trunk muscles.

Reflexes. Both pupils showed the Argyll-Robertson sign. The knee- and ankle-jerks were absent. Abdominal and epigastric reflexes brisk and equal. The plantar reflex gave the flexor response. Both urine and faeces were voided involuntarily, but consciousness of the acts was retained.

The cranial nerves were normal, with the exception of some pallor of both optic disks; this was probably due to early atrophy, for though vision in each eye was equal to $\frac{6}{9}$, the visual fields, especially of the right eye, were certainly contracted.

Sensation. There was but little loss of sensation. Light touches were well recognized, except over the upper thoracic region, where, on testing with cotton-wool, a distinct girdle of anaesthesia was present. Undoubtedly also the legs were analgesic in places. No pain was elicited on firm pressure of the testicles. Differences in weights and the position of the segments of the limbs when they were passively moved were well recognized.

Progress. The patient died after being in hospital for ten weeks. Various methods of treatment were tried, including mercury and iodide, without the least success in arresting the downward course. Severe pain in the abdomen, associated with flatulence and vomiting, relieved only by morphia, exhausted the patient, and this, aided by increase of the ataxia, brought him to a bedridden condition.

The tremor and unsteadiness of the upper limbs also increased to such an extent that for some time before death he had to be fed. The loss of control over the sphincters completed the total incapacity, and the patient finally sank in stuporose delirium.

Cerebro-spinal fluid. The chief characteristic was the great increase of protein content. On boiling, a dense opaque precipitate occurred. The ammonium

sulphate test (phase I of Nonne and Apelt) was markedly positive. Lympho-cytes, though increased, were not markedly so. (Wassermann's reaction not done.)

Post-mortem. The viscera other than the nervous system were normal. On exposing the spinal cord it was at once seen that the chief lesion was a massive spinal lepto-meningitis; its maximum extent was over the cervical region, where the cord was encircled by the semi-gelatinous, and in places tough, newly-formed tissue. At this region the thickened meninges measured as much as 5 mm. Anterior and posterior aspects of the cord appeared equally affected. Above and below the cervical region the meningitis was present, but the amount of the thickening greatly diminished, so that in the lower lumbar region its presence was only certainly demonstrated by the microscope. Cross sections of the cord showed plainly that it was much smaller than normal.

A microscopical examination of the spinal cord and medulla was made, and sections stained in the usual ways. Briefly the findings were :—

1. Characteristic meningitis with pronounced syphilitic vascular changes and great distortion of the form of the cord by the growth.

2. Scattered diffuse changes in the white and grey matter of the cord, chiefly found at the place of maximum intensity of the meningitis.
These were vascular dilatations and minute haemorrhages and spreading of the specific inflammation into the cord along the pial septa.

3. Endarteritis in the brain.

4. Certain degenerations in the cord.

(*a*) *In the posterior columns*, the most extensive change was found at the level of the third lumbar segment, and, as shown in Fig. 1, occupied the area of the bandelettes externes, where normally there are the fibres which form the afferent spinal reflex and afferent cerebellar systems. The picture shown at this level was, therefore, very like that of early tabes. The degeneration could be followed upwards as far as the mid-dorsal region, gradually to approach the grey commissure (Fig. 2). About this region the distortion of the cord, owing to the pressure of the massive meningitis, became so great that it was difficult to trace the degeneration. At the cervical region, however, there was a typical degeneration in the root zone (Fig. 3). In no place could a well-defined degeneration be seen in Goll's column. The degeneration in the root zone could also be followed to the lowest sacral region (Fig. 4).

(*b*) *Pyramidal tracts.* A marginal degeneration especially affecting the pyramidal tracts was seen throughout the sections.

5. The extra-medullary posterior roots and the fine fibres of Lissauer's tract were degenerated.

6. The Marchi stain yielded no evidence of a recent system degeneration, but numerous scattered degenerating fibres were seen.

7. Nissl's stain showed no special change either in the ventral cornual cells or in the spinal ganglia.

Clinically this case presented symptoms strongly suggesting tabes as the diagnosis; pathologically the chief lesion was widely-spread meningitis and vascular disease, both no doubt due to syphilis. A number of generally similar cases have been recorded, and the possibility that a syphilitic lesion may cause symptoms very like those of tabes recognized, hence the name applied to them of syphilitic pseudo-tabes. Their practical interest is considerable, for the accurate diagnosis and consequent treatment may be of importance.

Diagnosis.

It appears that in a minority the diagnosis may be impossible, or at least extremely difficult. Thus in Collins's case there were neuralgic shooting pains of three years' duration, disturbance of urogenital functions, ataxia of station and locomotion, diplopia, hypalgesia, hypaesthesia and ulnar anaesthesia, Argyll-Robertson pupils and hypotonia, and loss of knee- and ankle-jerks. Yet the post-mortem findings did not show any of the lesions of tabes. The patient died from acute Bright's disease.

On the other hand, certain symptoms may suggest that we are not dealing with simple tabes. Nonne, Collins, Oppenheim, and other writers lay stress upon the rapid development of symptoms and early onset after the acquired disease. A rapid change in the grouping of the symptoms, indicating a shifting in the site of the maximum intensity of the diseased process, especially the erratic behaviour of the knee-jerks; the presence of paresis or paralysis; the presence of optic neuritis or of cerebral symptoms of syphilis; the total paralysis of the pupil, rather than the presence of the Argyll-Robertson pupil; unilateral pupillary abnormalities—are suggestive of syphilis, and so also may be permanent ocular palsies. If, with the symptoms of tabes, sudden alterations in the clinical picture occur; if muscular weakness, paresis, spasticity, and anomalous pupillary signs develop; then syphilis (syphilic pseudo-tabes) may be suspected, or indeed definitely diagnosed. (See also *System of Syphilis*, vol. iv, p. 176, by Mott.) To the general rule that tabes occurs at a late interval, and syphilis early, after the acquired disease, there can be no doubt exceptions; but it is important to remember that a late syphilitic affection is more common than an early tabetic lesion.

A point of great importance is the presence of the Argyll-Robertson pupil. On the one hand, about 70 per cent. of cases of tabes show this sign: on the other hand, Michell Clarke found that it was present in syphilis in only five out of forty-eight, i. e. about 10 per cent.; D. K. Henderson in two out of twenty-three, i. e. 8·6 per cent.; and the remarkable statistics of Siemerling give only 1 per cent. in which the sign was present in cerebro-spinal syphilis. The records, however, of the class of case now under consideration show that this sign is frequently mentioned as being present. I have been able to read the original records of the following twelve cases. In all there were gross lesions of the meninges and cord, together with some posterior column degeneration. I give the opinion of the authors as to whether this lesion was tabetic or not. Opinions may differ as to this, but it appears important to note that *the presence of the Argyll-Robertson pupil cannot negative the diagnosis of syphilis added to a lesion which may or may not be true tabes.*

Collins, Ewald, and Schwarz (three cases) believe that in these cases it is non-tabetic; Valentin, Dinkler, Pick, Kuh, and Panegrossi believe that it is tabetic; Warrington that it is probably tabetic, and Brasch that it is not definite.

Cerebro-spinal Fluid.

The generally accepted rules are : 1. Lymphocytosis is most marked in the parasyphilitic affections (Michell Clarke). According to Mott, the lympho-cytosis in early parasyphilitic affections is, as a rule, not so great as in syphilis. In tabes the reaction is not affected by mercurial treatment, whilst in syphilis it disappears. 2. Most workers with the Wassermann reaction agree that this is much more common in the cerebro-spinal fluid in the parasyphilitic affection than in syphilis. Clarke's analysis gives : In general paralysis, positive in 100 per cent. In tabes, positive in 80 per cent. In cerebro-spinal syphilis, positive in 3·7 per cent. There certainly appear to be some exceptions— D. K. Henderson mentions several—further, the reaction, being quantitative only, may be and has been found in diseases which have no relationship to syphilis, e. g. endothelioma of the brain. In another case a glioma of the brain and a gumma of the liver were present.

Pathology.

The special interests attaching to these cases from the pathological aspect are : What is the nature of the degenerations in the conducting tracts ? Are they those of true early tabes ? Or are they secondary to the meningitis, and does their study throw any fresh light upon the problem of the genesis of tabes ? Several writers claim that the changes found in the posterior columns in the cases they record are true tabetic degenerations ; amongst others, Valentin, Pick, Kuh, Dinkler, Sachs, and Panegrossi. The chief fact they rely upon is that the degeneration was uniform throughout a long vertical extent of the cord, whereas the degeneration due to implication of the posterior roots is characterized by its diffuse and irregular distribution. The latter feature is well shown in the figures which illustrate Eisenlohr's paper. Here a general diffuse meningitis was present over the posterior surface of the cord, especially well marked at the level of the eighth dorsal vertebra, and at this place there was a marked affection of the posterior columns and roots, but the whole vertical extent of the degeneration measured only 1½ cm. ; the changes existing beyond this limit were irregularly scattered.

A priori, the independent appearance of the tabes with syphilitic meningitis is not unlikely, for on the one hand Adrian has shown that tabetics not infrequently suffer also from true syphilitic lesions of the skin and viscera, and on the other hand meningitis does not often cause such damage in the roots as to lead to gross degenerations. Thus in one of the earliest published cases of this kind, namely that by Oppenheim, there was gummatous disease of the posterior roots, but the posterior columns were not especially affected.

If the origin of tabes as secondary to any form of meningitis were accepted a considerable impetus would be given to the employment of the specific remedies. The generally accepted view is opposed to any such supposition. It

is more commonly believed that the tabetic degenerations are due to certain noxious influences, of unknown nature but generated by previous syphilis, which attack a certain part of the sensory protoneurone; and that this part is the stretch of nerve fibre from the point where the posterior roots, losing their neurilemma sheath, penetrate the pia mater—the ring of Obersteiner—to their terminal fibres around Clarke's cells and the ventral corneal cells. It is not known whether the degeneration spreads from within outwards, or in the opposite direction.

The objections to the meningeal theory chiefly advocated by Redlich, Obersteiner, and the French school are many and well known. The subject is fully discussed in Ferrier's Lumleian Lectures for 1906. He goes on to say, 'Nor is meningitis, syphilitic or otherwise, when it does occur, a common cause of intraspinal degeneration by implication of the posterior roots. That such a result is possible, and perhaps actually occurs in some cases, may be admitted, but it is extremely rare.' The cases we are now considering, if the lesion is not primary incipient tabes, would belong to this category.

Schwarz has attempted to show that here there is an actual infiltration of the roots with syphilitic tissue, and that this differs entirely from the thickening of the endothelium of the pia mater so often found in tabes, and is also fundamentally different from the meningeal change described by Redlich and Obersteiner. This explanation would perhaps explain the peculiar and striking clinical resemblance to tabes. The degenerations sometimes present in the pyramidal and other long conducting tracts are probably due partly to the strangulation of nutrient blood-vessels, and partly to the presence in the cord itself of syphilitic processes.

Treatment.

Cases of syphilis so closely resembling tabes as to cause much hesitation in the diagnosis to the ordinary well-informed observer are certainly very rare. Spinal syphilis, if we exclude at any rate sudden syphilitic myelomalacia—'acute myelitis '—is itself uncommon. In Williamson's monograph it is stated that in ten years only thirty-two cases were diagnosed in the Manchester Royal Infirmary as spinal syphilis. Only one of these closely simulated tabes. It is probably correct to say that cerebral and spinal syphilis is fairly amenable to the effects of properly administered mercury and iodide, but in considering the special form of syphilis, the pseudo-tabes, it is suggestive that it was after the post-mortem findings that the significance of the clinical resemblances was first appreciated. In fact, nearly all the papers dealing with this subject have been based upon pathological findings. The lesion found has always been one of great severity, and in a number an energetic anti-syphilitic treatment had been carried out.

I am inclined to think that in this group of syphilitic nervous diseases the prognosis is especially grave. Signs of bad omen appear to be the onset of general emaciation, local atrophy or spasticity, the presence of intense localized

pain, and of course symptoms such as were present in Oppenheim's cases indicating invasion of the medullary centres, and a late onset after the acquired disease.

If 'Salvarsan' is to be of special service as a preferential treatment in nervous syphilis, it may well be used in such conditions.

Apart from the severe cases which are recorded after post-mortem examination, a number of much less severe ones have been mentioned ; these chiefly occur soon after the primary disease, when fortunately suspicion as to their real nature is aroused. Many of these have been quickly cured. Probably the chief therapeutic lesson taught by cases like mine is the need for caution in giving the diagnosis of tabes when either the history or symptoms are atypical in early cases.

It is not improbable that after the distinctly enthusiastic manner in which Risien Russell and F. Buzzard spoke on the treatment of tabes by mercury, at the London meeting, 1910, of the British Medical Association, anti-syphilitic treatment will again be thoroughly tried in this country. In France this has been for a long time the custom. In this country it must be remembered that many accept the view of the meningeal origin of tabes, and they can, therefore, refer to pathological teaching as a justification. Most pathologists in England, America, and Germany, however, feel it difficult to believe that the symptoms due to the tabetic lesion as contrasted with the tabetic person can be permanently improved by anti-syphilitic treatment. It appears desirable in the interests of diagnosis, therapeutics, and pathology that detailed accounts of successful cases should be published.

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SINUS ARRHYTHMIA OF HIGH GRADE INDUCED BY DIGITALIN

By E. E. LASLETT

In this paper the writer records three cases in which, with a normal rhythm, a notable slowing of the whole heart was induced by the administration of digitalin. This reaction appears to be rare. The slowing effect of digitalin on the pulse-rate is obtained most readily in certain cases of auricular fibrillation, and when the normal rhythm is present an abnormally infrequent heart-beat induced by the drug is more commonly an expression of heart-block than of slowing of the whole heart. The appearance of this reaction in any one patient is, however, variable and somewhat fleeting, and it is possible that with extended observation it may prove to be more common than has hitherto been believed. On the other hand, Mackenzie, in his recent paper recording detailed observations on the action of digitalis on a series of patients, mentions only one case among those with normal rhythm in which there was marked slowing apart from heart-block, although some degree of sinus arrhythmia was observed in a number of the cases. The same writer has published a striking instance of this reaction in a patient suffering from mitral stenosis. On one occasion a pause of nearly four seconds' duration was observed. A similar case has been recorded by Lewis. In both of these patients there was a pre-existing impairment of conductivity as shown by a wide a–c interval. In the former conductivity was not further depressed by the digitalin; on the contrary, after the long pauses the a–c interval was much diminished. In Lewis's case sinus arrhythmia was not the only irregularity observed, for sometimes conduction from auricle to ventricle became so impaired that ventricular beats dropped out.

In two of the cases here considered there was definite evidence of an impairment of conductivity. Notwithstanding this, digitalin did not further depress conductivity, or, to speak perhaps more accurately, the grade of heart-block was not increased sufficiently to cause ventricular silences.

Case I. Mitral Stenosis. Female, aged 19 years. She was first seen by the writer in June, 1909. When nine years old she had scarlet fever, followed apparently by nephritis. There was a history of growing pains in childhood, but not of definite rheumatic fever or chorea. She had, however, had one slight attack of rheumatism since she had been under observation. She first became aware in 1906 that she had heart disease.

Condition, June, 1909. There was slight but definite cyanosis of the lips, nose, and ears. She was comfortable when sitting or lying down, but she

became breathless on very slight exertion. She was unable to mount a flight of about twelve stairs in her house without stopping two or three times, and she could not walk more than fifty yards without a rest. The pulse was quick and irregular owing to the frequent occurrence of auricular extra-systoles. With inspiration the pulse became very weak ; often indeed it could not be felt, particularly on the left side. If the breath was held after a deep inspiration the pulse disappeared completely, as shown by the sphygmograph ; but when she was able to hold the breath long enough the pulse returned feebly before the respiration was resumed. The heart-impulse was diffuse. The apex-beat was just outside the nipple line, where the movement was feeble. The greatest amplitude of movement was over the fourth and fifth ribs, between the nipple and the left border of the sternum. A positive cardiogram was readily obtained over this area. There was a presystolic murmur at the apex, accompanied by a very slight thrill. Here both sounds were loud. There was a systolic murmur all over the praecordium. The second sound was loud at the pulmonary area. The veins of the neck were pulsating. Curves of the venous pulse taken at this time showed a clear auricular wave with the a–c interval perhaps slightly increased. The liver was enlarged and pulsatile, and gave a curve of the auricular type.

Progress. After a few days the irregular heart-action disappeared and it has not been observed since. Rather more than a year ago two important changes occurred in the condition of the patient. In the first place the venous curve showed a striking change in the development of a well-marked double peak in the presystolic wave, and since, as will be shown later, the first part of the wave is certainly due to the contraction of the auricle, there was a coincident widening of the a–c interval. In the second place the presystolic murmur disappeared. Recently, however, it has been observed that when the breath is held after inspiration a definite short presystolic murmur appears, limited to the apex area. It disappears as soon as breathing is resumed. During the suspended respiration it may be that opportunity is given for the over-distended left auricle to partially empty itself, and thus contract more forcibly. The possibility of the left auricle being over-distended and paralysed while the right remained active has been suggested by Lewis.

Apart from these changes the patient has remained in about the same condition as when first seen. At intervals some oedema of the lower extremities develops, but this has usually disappeared under the influence of digitalis or one of its allies, without rest in bed. Digitalis, strophanthus, and squills have been given frequently, in each case in the form of the tincture. Not one of these drugs given in this form has been able to reduce the pulse-rate below 70. Frequent observations were made and numerous curves taken in order to detect any change in the rate of conduction from auricle to ventricle. No change could be found, and the dropping out of ventricular beats was never observed. As an example, digitalis (45 minims per day) was taken for a fortnight. Little or no change in the pulse-rate occurred. Owing to the onset of diarrhoea tincture of opium in 5 minim doses was then added to the prescription, which was continued for another two weeks. The general condition of the patient improved, but the pulse-rate fell only to 70 per minute.

Recently, for three separate periods, Nativelle's granules of digitalin (gr. $\frac{1}{240}$) have been prescribed, two per day. On each occasion marked slowing of the pulse appeared, accompanied by sinus arrhythmia. The irregularity appeared on the first and third occasions after 20 granules, on the second occasion after 14 granules had been taken. Coincidently with the onset of the irregularity the patient experienced nausea and vomited, and the drug was withdrawn completely or continued in half doses. In either case the pulse resumed its normal rate at the end of three days.

The Jugular Venous Curve.

This is illustrated in Fig. 1. There are two presystolic waves separated by a deep depression. It was at first considered possible that the first peak might be either an unusually well-developed *h*-wave or a fusion of this with the first part of the auricular wave (Windle). There were weighty reasons against this interpretation, but the origin of the first peak was finally proved to be auricular, when it was found that the relation of the two peaks to each other was unchanged when the pulse-rate fell to 50 or even 40 per minute, under the influence of digitalin. In some published curves with a wide *a–c* interval there is occasionally an indication of a second wave between *a* and *c*, but such a well-marked bifurcation as the present case shows seems to be unusual. Cowan and
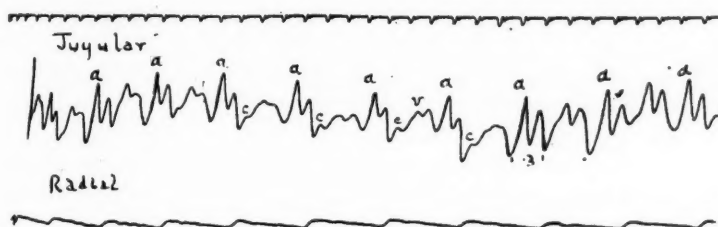
Fig. 1.
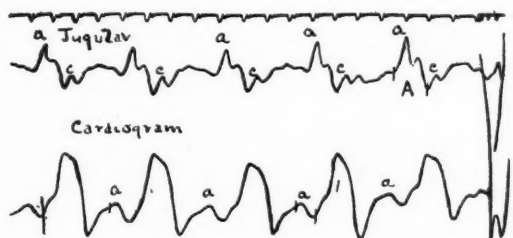
Fig. 2.

Ritchie have published a curve which probably shows the same condition. The auricular wave in the liver pulse commences just appreciably later than the upstroke of the first peak of the jugular pulse. The wave is unusually broad and in a good curve shows a slight indentation at its summit.

The cardiogram (Fig. 2) shows a small presystolic elevation followed by a deep depression. The upstroke of the elevation occurs at the same time as the first wave in the jugular pulse, and must therefore be due to the auricular systole. In some of the curves the presystolic dip is small or absent, and then there is a single broad wave (Fig. 8). The *As–Vs* interval with normal rate equals a full fifth of a second. The ascending limb of the ventricular portion of the cardiogram shows always a distinct shoulder, which becomes more pronounced when the breath is held. This appears to be identical with the *i*-eleva-
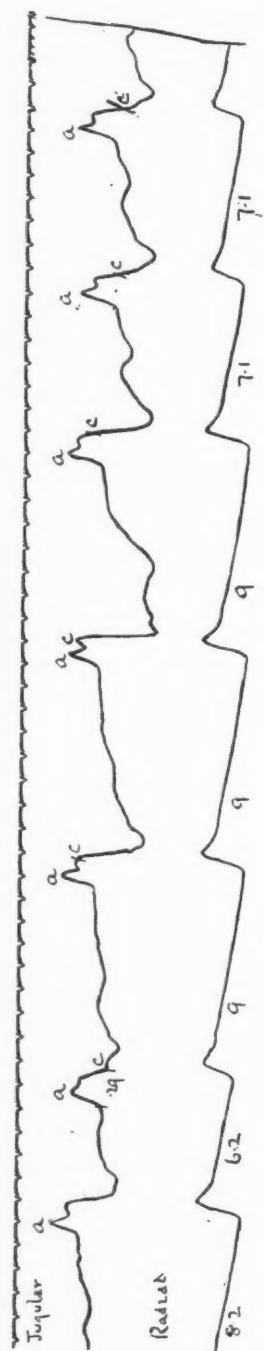
Fig. 3.
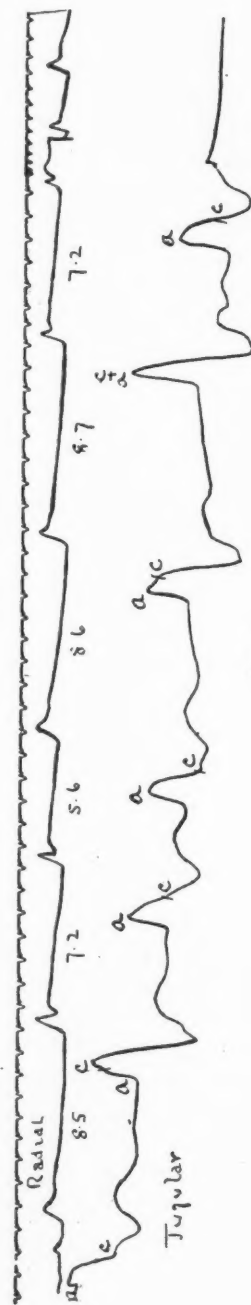
Fig. 4.

tion of Robinson and Draper. The termination of this wave appears in this case to mark the end of the presphygmic period; there is, however, a considerable margin of error with the comparatively slow movement of the recording paper, and these authors consider that the i-wave bears no relation to the presphygmic period of the ventricular systole.

As already mentioned, the disappearance of the presystolic murmur originally present would indicate the existence of over-distension and paralysis of the left auricle. This being so, it is probable that the presystolic wave in the cardiogram is caused by the right auricle.

The first of the presystolic waves in the jugular pulse is undoubtedly auricular in origin. To what, then, is the second wave due? In favourable cases a faint wave is sometimes found in the jugular pulse which is synchronous with the i-wave in the cardiogram, representing the so-called inter-systole. The second wave in this case, however, commences at a distinct interval before the upstroke of the cardiogram. Further, with the varying rates observed under the influence of digitalin the relation of the depression between the two waves to the calculated position of c varied considerably, much more in fact than could be accounted for by variations in the presphygmic period; while the relation between the depression and the upstroke of the first wave remained practically constant. Expressed in another way, with the slower rates the presystolic wave moved forward as a whole relatively to the position of the corresponding radial wave. This is well shown in Fig. 3. It is probable therefore that the second wave is partly at least due to the contraction of the auricle. The prolongation of the auricular wave in the jugular curve and the presence of a prominent broad wave in the liver pulse are probably the expression of hypertrophy of the right auricle.

Sinus Arrhythmia.

The onset of the irregularity has been preceded on each occasion by a regular slowing of the pulse-rate to about 60. Then occasional longer pauses appear, and with a very small additional quantity of the drug the typical arrhythmia appears. It is not constantly present. One finds that there are often long intervals during which the pulse is nearly regular and moderately slow. The arrhythmia is frequently induced by forced breathing, or by holding the breath after inspiration. It has, however, no fixed time relation to the respiratory movements; the phasic variations in rate are of much longer duration than that of a respiratory cycle. Thus, to give an extreme example, for a period of 18 seconds the pulse-rate averaged only 40 per minute. The longest pause hitherto observed has been $\frac{11}{5}$ seconds.

The condition of the conductivity of the bundle when the heart is beating slowly deserves special mention. It would be expected that as a result of the lengthened period of rest the conductivity would improve and the a–c interval diminish. This was not found to be the case (Figs. 3 and 4). After the

longest diastoles it is true that the $a-c$ interval usually diminishes or becomes normal, but a number of exceptions to this rule were met with. A good example of this is shown in Fig. 3, where after the third long pause conductivity is clearly delayed. When the pause is not longer than $\frac{7}{8}$ seconds the $a-c$ interval is almost invariably longer than normal. The cardiogram in Fig. 7 affords further evidence on this point. The $a-v$ interval after the long pause remains
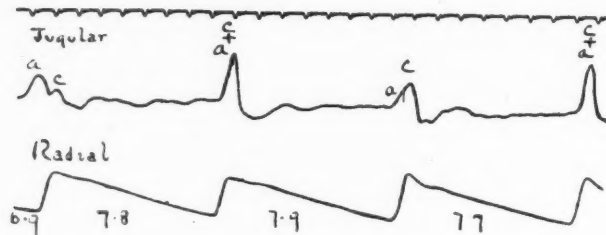
FIG. 5.
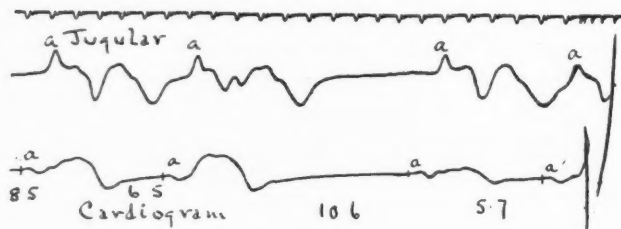
FIG. 6.
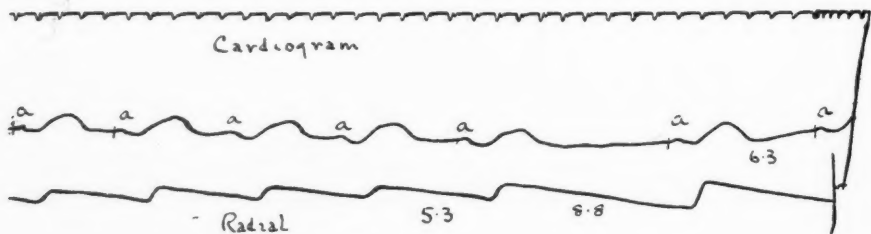
FIG. 7.

wide, although it is possible that it is somewhat exaggerated in the figure. The upstroke of the ventricular portion of the cardiogram appears to be too much delayed, possibly from a mechanical fault. It must, however, be borne in mind that after such a long diastole the presphygmic period may be diminished (Robinson and Draper), and the shortening of the $V-R$ interval may be partly or wholly due to this cause. This is borne out from an examination of other cardiograms where there are series of slow beats.

Idio-ventricular Contractions.

When the auricular pauses become sufficiently long it may happen that the ventricle contracts before the auricle from an intrinsic impulse. These ventricular contractions have been carefully studied by Lewis. They frequently appeared in this patient, instances of which are illustrated in Figs. 4 and 5. The pulse-beats are judged to be due to ventricular contractions of intrinsic origin, when a precedes c by a very short interval (second beat in Fig. 4), or a practically coincides with c, with a resultant large wave (sixth beat, Fig. 4). Occasionally the auricular contraction occurs later than and quite separate
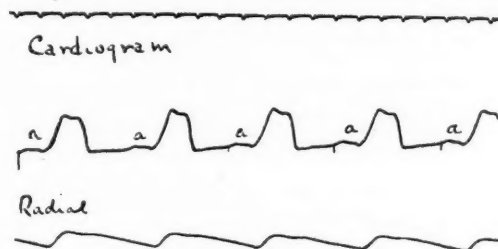
FIG. 8.

from the ventricular. The length of the pause preceding the idio-ventricular contractions has varied in this patient from $\frac{7 \cdot 7}{5}$ to $\frac{9 \cdot 2}{5}$ seconds, representing a difference of rate of about seven per minute. Lewis also observed considerable variation in the rate of the idio-ventricular rhythm in his case. When the heart was beating slowly in the present case the patient occasionally experienced a sensation of 'thumping' in the chest. It appeared to the writer that this sensation occurred particularly when the auricles and ventricles contracted simultaneously.

Case II. Mitral Regurgitation. Male, aged 66. A stout, florid man. He had scarlet fever when 12 years old, and had had three attacks of rheumatic fever. He had had good health on the whole, had been a great swimmer, and had led an active life. Apparently the heart had well maintained its vigour, and the present appeared to be the first serious breakdown.

Condition, July, 1911. The face was somewhat cyanosed. The patient was very short of breath and became still more breathless and exhausted on the least exertion. There was considerable oedema of the lower limbs. The pulse-rate was 80. The beat rose sharply under the finger, but it was ill-sustained. The systolic blood-pressure was 155 Hg. (Hill). There were frequent intermissions of the pulse which were shown to be due to the occurrence of ventricular extra-systoles. After slight exertion the pulse became alternating in character. The apex-beat could not be felt and it was impossible to map out accurately the cardiac dullness owing to the presence of emphysema. The first sound was feeble at the apex and was followed by a rather loud musical systolic murmur, and then by a feeble second sound. At the base both sounds were clear and free from murmur. The venous pulse in the neck was feeble, and

owing to the short stout neck and the presence of respiratory distress it was difficult to obtain a satisfactory tracing except for a short stretch of curve. The a–c interval was prolonged (0·3 second). The occurrence of ventricular extra-systoles enables one to exclude the possibility (well illustrated in this patient) of a wide a–c interval being simulated by the fusion of h- and a-waves, for in the pause following an extra-systole h is separate from a, and the a–c interval remains definitely increased.

Progress. The patient was kept in bed. Digitalin granules were prescribed, two per day. He soon began to improve, and the pulse became less intermittent. At the end of a week, when he had taken fourteen granules, his breathing was much easier and the dropsy had disappeared, but he felt drowsy and stupid. The pulse was now very irregular and slow, the rate averaging 60. A venous curve showed that the irregularity was due to sinus arrhythmia, with long pauses of $\dfrac{6\cdot5}{5}$ to $\dfrac{7}{5}$ seconds' duration. The intermissions occurred usually one or two at a time independently of the respiratory movements, but if the breath were held there was often a series of five or six at a rate of 40 per minute. In this case also the conduction time of the a–v bundle, shown to be normally prolonged, was not diminished after a long intermission so much as might be expected. For example, after a pause of $\dfrac{\cdot6\cdot5}{5}$ seconds the a–c interval of the following beat was 0·3 second. It is not considered necessary to reproduce the curves ; they show no features not already illustrated from Case I.

The digitalin was reduced to one granule per day and continued at this dose for another week. In two days the pulse-rate had risen to 66, and the patient was brighter. Thereafter he continued to improve.

In the two cases just described it has been shown that even when the heart becomes greatly slowed the time of conduction from auricle to ventricle remains abnormally prolonged. This phenomenon would lead one to suppose that in addition to the general slowing effect induced by digitalin, probably through the medium of the vagus nerve, there is also an adverse influence on the conductivity of the a–v bundle. Mackenzie has shown that when conductivity is impaired digitalis commonly increases the defect and a higher grade of heart-block appears. That the latter form of irregularity was not induced in these patients and in Mackenzie's case may be due to the abnormal sensitiveness of the pacemaker of the heart to the action of digitalin, in consequence of which general slowing becomes the more prominent reaction to the drug and the supposed simultaneous action on the conducting system of the heart is thereby counteracted to some extent.

Case III. Mitral Stenosis. Male, aged 23. He had chorea when eleven years old and again at fourteen. He had a slight attack of rheumatic fever when 21, but he had been passed by his works doctor since. He had noticed lately some breathlessness when cycling, but otherwise had been well and was unaware that he had heart disease. He had not previously been under my care.

Present illness. On September 24, 1911, he was without food for some hours owing to the demands of his work. He became very exhausted, and was seized with a gnawing pain in the body. This continued for a week, but though he felt very ill he remained at work off and on till October 1.

Condition, October 1. He looked pale and distressed, slightly cyanosed; respirations 40. The tongue was very dry, and the temperature 100·6° F. The pulse was feeble, very rapid, and for the most part regular, but showed occasional longer pauses. It could not be counted, but a curve of the radial pulse showed a rate which often reached 170–180 per minute. The heart dullness was increased in both directions and there was a soft systolic murmur all over the praecordium. There was marked pulsation in the veins of the neck. The liver was enlarged and pulsating. In spite of the rapid breathing no abnormal signs could be detected in the lungs. He still had the gnawing pain in the body and felt very ill, but he had no sense of fluttering or palpitation in the chest.

A simultaneous venous and radial curve taken in the afternoon showed that there was no auricular wave in the normal situation. Short stretches of curve showed such regularity as to suggest a paroxysmal tachycardia, but there were occasional irregular intermissions, and nowhere could a normal auricular wave
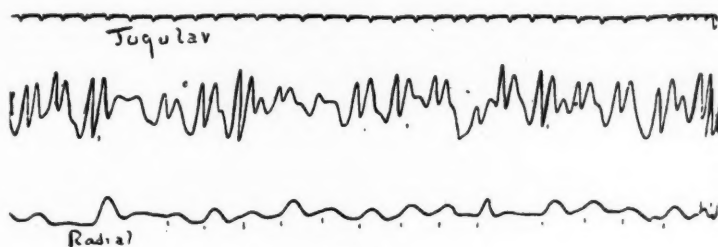
Fig. 9.
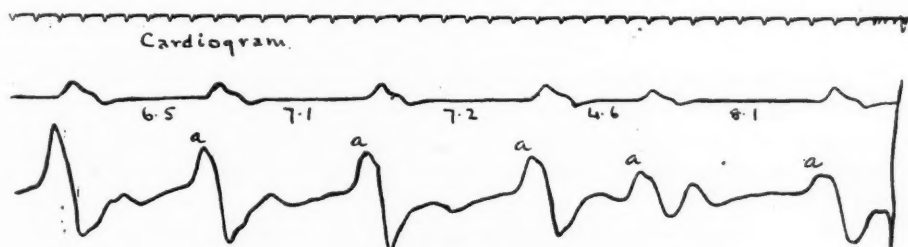
Fig. 10.

be recognized with certainty. It seems more probable, therefore, that the auricles were fibrillating (Fig. 9).

Shortly after I left him he became rapidly easier, probably owing to the return of the normal heart rhythm. In the evening he took two granules of digitalin. Next morning he was quite comfortable. The pulse-rate was 80, regular for the most part but showing occasional intermissions. The apex-beat was in the fifth space, two inches outside the nipple line. The dullness extended a little further to the left, and to the right it reached the right border of the sternum. The chest was rather narrow from side to side. There was a well-marked presystolic followed by a systolic murmur, audible only at the immediate apex area. Elsewhere over the praecordium there was a faint systolic murmur. At the base the sounds were clear. The liver appeared to have returned to its normal size and no pulsation could be detected. Two granules were taken during the day. A venous curve was taken in the evening after he had taken four granules of digitalin. The normal auricular rhythm was now present, and the *a–c* interval was $\frac{1}{5}$ second. The heart was irregular

owing to the presence of sinus arrhythmia, and there were also fairly frequent auricular extra-systoles. The arrhythmia was of the same character as in the cases already described. With natural breathing the long pauses of $\frac{7}{5}$–$\frac{8}{5}$ seconds appeared only occasionally, but if the breath were held the pulse-rate diminished to 40 per minute and under, although sometimes the rate increased to 60 towards the end of a long period of suspended respiration (Fig. 10). After the long pauses the a–c interval remained the same as with normal rate.

The dose of the digitalin was now reduced to one granule per day and continued so for a further two days. The pulse on the whole became still slower, varying in rate from 42 to 48. The longest intermission observed was $\frac{9}{5}$ seconds. The drug was then stopped, and two days afterwards the heart had returned to its normal frequency.

The slowing of the heart appeared in this patient after an unusually small quantity of the digitalin had been taken, and it might be suggested that it was not really induced by the drug, but was an expression perhaps of the exhaustion of the heart as a result of a sudden and prolonged tachycardia. Arrhythmia of such high grade is, however, rare. Further, the infrequency of the heart became greater and more continuous with the continued administration of the digitalin, while it rapidly disappeared after it was withdrawn. In order to obtain further evidence on this point the patient was again given two granules a day, commencing on October 15. The pulse was carefully watched and numerous curves taken. The first effect observed was an increased tendency to the development of a coupled rhythm, which had been frequently noticed in this case apart from all drugs. When he had taken twenty granules, exactly the same arrhythmia appeared as before.

As this reaction is in itself rare it is difficult to avoid the conclusion that the arrhythmia in the first instance was really due to the action of digitalin and not merely coincidental. If so, its appearance after such a small quantity of the drug may possibly have been due to a heightened sensibility of the sinus rhythm to the inhibitory influence of the drug at the offset of auricular fibrillation.

It is a pleasure to express my indebtedness to Dr. Mackenzie for kind help in the study of these cases.

Conclusions.

Three cases are described which developed sinus arrhythmia of high grade under the influence of digitalin.

Two of the cases had a pre-existing impairment of conductivity, notwithstanding which the grade of heart-block was not increased by digitalin so far at least as to cause ventricular silences.

The first case exhibited an unusually well-developed two-peaked presystolic wave in the jugular pulse. The first wave was undoubtedly and the second probably auricular in origin. The peculiar form of the wave is regarded as evidence of hypertrophy of the right auricle.

The third case showed an extreme sensitiveness to the drug, which, it is suggested, may have been in some way related to the fact that the auricles had just previously been in a state of fibrillation.

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DESCRIPTION OF FIGURES.

Detailed reference is made to these in the body of the paper. The time-marker indicates fifths of a second. The figures below the radial give the duration of the pulse intervals in fifths of a second. Figs. 1–8 inclusive are from Case I. Figs. 9 and 10 are from Case III.

AURICULAR FIBRILLATION ASSOCIATED WITH A HIGH DEGREE OF *A–V* BLOCK AND PAROXYSMAL TACHYCARDIA

By C. E. LEA

THE interest in the following case centres mainly over a period of three weeks, from October 26 to November 16, 1911, during which polygraphic tracings showed evidence of changes in the cardiac rhythm of unusual character. Notes of considerable value relating to this case are available, previous to this period, from the time of his first admission to the Manchester Royal Infirmary in April, 1909. Finally, after the patient's death, which occurred on December 22, 1911, a post-mortem examination was made, which enabled one to judge of the character of the circulatory and general organs. The patient was a man aged 55 at the time of his last admission to the Royal Infirmary on October 7, 1911. He was complaining of great shortness of breath, swelling of the legs and stomach.

Course of the illness. The progress of the illness, previous to this, his last admission to hospital, may be briefly noted. The patient first noticed that he was short of breath on exertion early in the year 1908. This was soon followed by swelling of the legs and stomach. He retired from his work as a blacksmith shortly afterwards. From April of the succeeding year, 1909, the patient remained a chronic sufferer from cardiac disease. He was an in-patient of the Infirmary on four occasions, April to June, 1909, January to March, 1910, January to March, 1911, and, finally, from October, 1911, to the time of his death in December, 1911. Always on his admission his symptoms were dyspnoea, oedema, and a variable degree of ascites. With rest and treatment he improved on each occasion except the last. The physical signs, as recorded in the notes of the case, showed progressive deterioration of the cardio-vascular system. On each occasion the pulse was pronounced irregular, and the first tracing, taken in January, 1911 (Fig. 1), shows the type of irregularity to be that which we know to be usually associated with auricular fibrillation. The area of cardiac dullness showed progressive enlargement, especially to the left. Thus, April, 1909, $\frac{\text{III}}{1\,|\,4\frac{1}{2}}$; January, 1910, $\frac{\text{IV}}{1\,|\,5\frac{1}{2}}$; January, 1911, $\frac{\text{IV}}{1\,|\,\frac{1}{2}\ \text{left of nipple line}}$; and in October, 1911, the same area of dullness was observed. The murmurs heard throughout the course of the disease were a systolic murmur replacing the first sound and a reduplicated second sound at the apex. A 'bruit de galop' was mentioned often in the notes. On his last admission to hospital there were no murmurs, the heart sounds were weak and distant, but the first sound was

slightly accentuated.   Additional signs of the increasing gravity of the patient's condition were: Some enlargement of the liver, which was also tender, first noted in January, 1911.   Oedema and ascites were present on all occasions.   The former usually passed off with rest; for the latter, paracentesis was first performed on October 9, 1911, and 156 ounces of clear fluid removed.   There was albumin in the urine on all occasions.   The chief point in connexion with the effect of treatment was the slowing of the pulse which resulted after the patient had been some time in bed.   Always he was given some digitalis preparation, and to the effect of this may, in part, be attributed this slowing (Fig. 2).

One feature in the sphygmographic tracing taken in January, 1911, was the frequent bigeminal character of the beats, a common feature associated with auricular fibrillation.   These 'extra-systoles' will be afterwards referred to. From the above facts, we may reasonably conclude that the case was one of progressive myocardial failure, associated with, and probably induced by, the disorderly action of the auricle.   Throughout the whole of the observations the pulse was never regular, and one may conclude that the auricular fibrillation, once induced, was, as is commonly the case, persistent.

Previous medical history.   The patient had never had rheumatism.   Venereal disease was denied.   His general condition previous to his illness was good.

Social history.   The patient was a married man, and had a family.   He had taken alcohol in moderation.   His work necessitated much muscular effort.

Family history.   His mother had died of 'dropsy'.   Father dead—cause unknown.   All children living.

Progress.   Patient was admitted to the Manchester Royal Infirmary, under the care of Dr. Judson Bury, on October 7, 1911, with urgent symptoms.   The ascites was relieved by paracentesis, and 156 ounces of fluid removed. There was some cyanosis; the breathing was laboured.   The pulse was rapid, irregular, 132 on admission, but slowed down rapidly within the next few hours.   There was marked oedema of the legs and genitals.   The heart dullness was $\frac{\text{III}}{1\,|\,5}$.   The sounds were weak and distant.   There was slight accentuation of the first sound over the apex.   There was some pulsation of the veins in the neck, the apex beat was neither visible nor palpable.   Two days after admission, the pulse had fallen to 96, and for the next thirteen days varied between 96 and 104 per minute. Digitalis infusion, two drachms, four-hourly, was given from October 7 to October 20. From October 18 to October 23 the breathing was very distressed.   Amyl nitrite seemed to give temporary relief.   Cheyne-Stokes breathing was noted on October 18.   On October 21 the digitalis was changed to tincture of strophanthus, 15 minims, four-hourly.   On October 25 the pulse was counted by the nurse during the day—40, 26, 70, and 66.   No note was made of the rhythm.   On October 26, at eleven in the morning, a tracing of the pulse was being taken by Miss May (Fig. 3) when the patient had a sudden and severe attack of syncope. This attack was associated with convulsive movements and lasted for a few seconds, though the distress of breathing lasted for several hours and there was

A.   B.
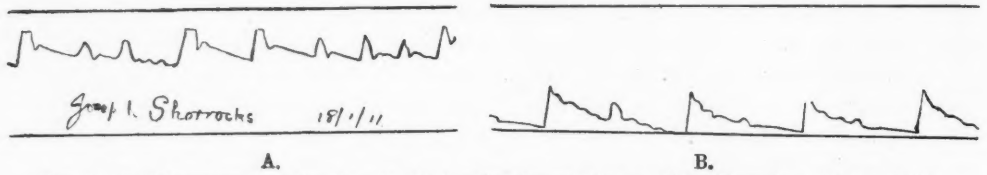
FIG. 1. A. Sphygmogram taken Jan. 18, 1911, pulsus irregularis; B. Shows bigeminy. Feb. 2, 1911.
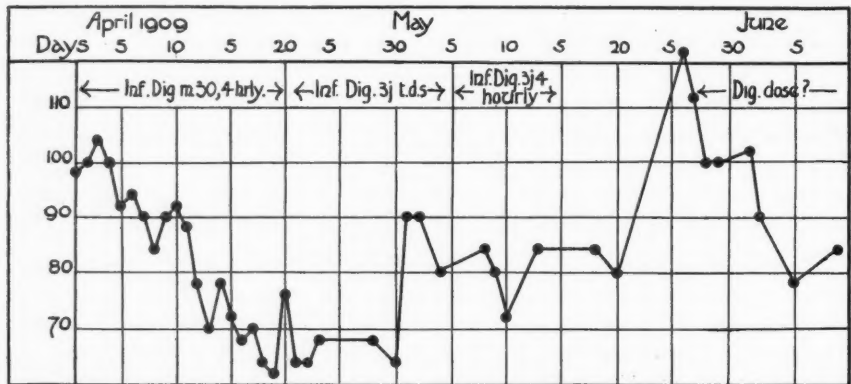
FIG. 2. Effect of digitalis upon pulse frequency.   Each dot represents the pulse frequency per minute, and each day is represented by one dot, since the frequency was only taken once daily. The numbers at the side represent beats per minute. Thus, for example, on April 5 the pulse frequency was 72 per minute; on May 30, only 64; and so on.   Above is shown the dosage of digitalis.
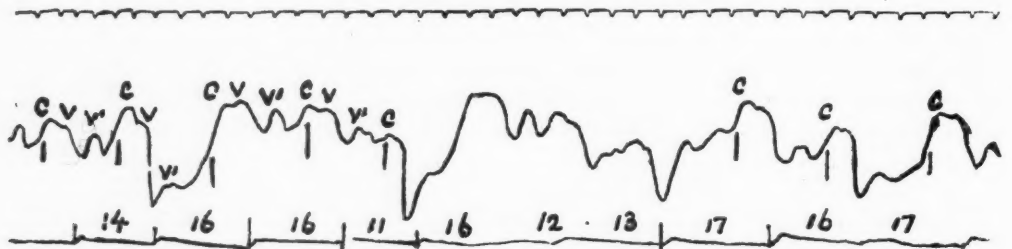
FIG. 3. Polygraphic curve immediately preceding the syncopal attack, Oct. 26, 11 a.m.   Time in fifths of seconds.   Lengths of cycles in twentieths of seconds (throughout).
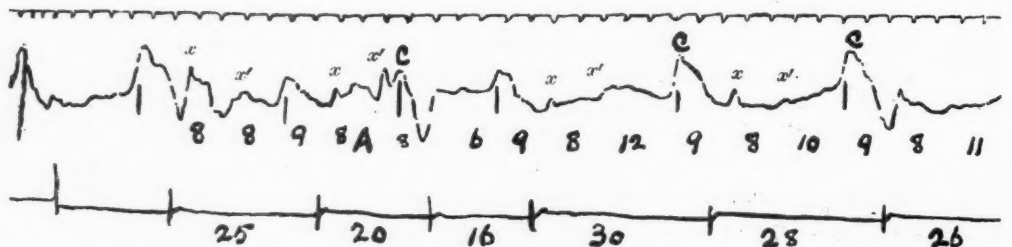
FIG. 4. Curve immediately after syncopal attack.   Note waves x and x', simulating auricular contractions.   Numbers in top row represent time intervals between x waves.

obvious distress in the patient's condition, for which an injection of morphia, 3 minims, was given, and was followed by relief of the subjective symptoms. At the time of the attack the pulse was counted at 40, and seemed, to the finger, to be regular. Shortly after the syncopal attack I obtained the tracing shown in Fig. 4. In comparing the tracing taken just before and immediately after the attack it is noted that there is a considerable difference. In Fig. 3 the separate cycles vary in length from 0·64 to 0·9 second. The double-peaked character of the v waves gives the appearance, in the tracing, of there being a definite a wave due to auricular contraction, if one accepts the second peak as due to auricular systole. The evidence, however, that such is not the case is, we think, shown by the fact that its distance from the preceding first wave is identical throughout the series, and that the variation in the length of the cycles is at the expense of the period between the second v wave and the succeeding c wave. The degree of arrhythmia is not great. The distance between the two peaks of the v wave is certainly greater than is usually the case, and there still remains the possibility that the second of these waves is an extra-systole, a point to which we will have occasion to refer again. In the tracing taken just after the attack the most marked feature is the slowing of the pulse. The ventricle is beating at a frequency of 36 to 43. There is still ventricular arrhythmia. The venous tracing is peculiar and its interpretation is not easy. It resembles at first sight a case of typical complete heart-block, for in the venous tracing, between the c waves, there are well-marked intermediate waves. Such waves, however, present an irregular sequence. Between the c waves two of these waves occur in most of the cycles. The distance between the first wave and the next is the same as that which separates it from the preceding c wave, 0·4 second. From the second x wave to the next c wave is variable, being, in succession, 0·4, 0·4, 0·2, 0·3, 0·6, 0·45, 0·45 second. As in Fig. 3, therefore, the ventricular arrhythmia is due to variations in the length of pause between the last wave in the cycle and the succeeding c wave. Against the view, therefore, that this is a case of typical heart-block is (1) the ventricular arrhythmia and (2) the irregular spacing of the x waves in between the c waves in the venous tracing. The character of the two x waves is different in each cycle. The first is always larger than the second. The relation between the c wave and the two succeeding x waves seems to be definite, for in the short cycle, marked at A, the second x wave immediately precedes the next c wave, but does not seem to influence it in any demonstrable way. We may conclude that the first wave x is probably an ectopic beat, arising in either the ventricle or the nodal tissues, and which does not affect the radial pulse. That such ectopic beats are frequent in this case is evidenced both from the previous sphygmogram, taken in January, 1911, where the bigeminy, associated in this instance with ventricular arrhythmia, is present, and from succeeding tracings, presently to be noted, in which such beats occur both singly and successively (tachycardia). The tracing in Fig. 4, then, represents auricular fibrillation, marked blocking at the junctional tissues, and frequent ectopic beats, having their origin probably in either the ventricle or the junctional tissues.

E e 2

The extent and degree of the compensatory pause, which one expects following ectopic beats of ventricular origin, is in a case such as the present confused by the probable multiplicity and variety of the stimuli and their sources, which are eliciting ventricular response.

Following the alarming syncopal symptoms the strophanthus was stopped. The next day the patient was better and the breathing was no longer troublesome. Tracings taken on October 28 showed the typical characters of auricular fibrillation. The pulse frequency was 78. The patient felt quite comfortable. Two days after, October 31, there was a change for the worse in his condition. The pulse was irregular at 96 (Fig. 5), there was increased oedema, and breathing was less easy. At 6 p.m. the patient was given the first dose of tincture of digitalis, 15 minims, which was continued from this date till November 8 (eight days). On November 1 the patient felt much better, the breathing was less difficult. The pulse had fallen to 90, and on November 3 to 80. Auricular fibrillation was still present. On November 5 the tracing showed several features which had not been previously observed. There were frequent periods over which the pulse presented regularly recurring extra-systoles, visible in the radial and all of equal distance from the preceding normal beat in the cycle, 0.65 second. The ventricle was beating irregularly. Whilst I was taking the tracing the patient began to have an exaggerated form of Cheyne-Stokes breathing. The culminations of the hyperpnoeic periods were associated with dyspnoea, almost anginal in its distress and intensity. The apnoeic periods were marked by comparative ease, but during them the patient expressed a very real dread of another 'attack'. The pulse tracing was taken continuously through both periods, but the difficult breathing during the hyperpnoeic periods prevented one getting satisfactory venous tracings. On several occasions, just before the onset of the apnoeic period and when the suffocation seemed at its height, the tracing showed that the heart suddenly broke into a condition of tachycardia, and with the offset of this rhythm to the usual irregularity the renewed difficulty of respiration began. Not all attacks of apnoea, however, were associated with tachycardia. In one instance, during the quiescent period of breathing, the pulse showed the arrhythmia of auricular fibrillation, but the degree of such arrhythmia was of greater intensity. This was noted on November 7, when other tracings showed that the same condition prevailed (and the following details apply to both dates). In one instance the apnoeic period was associated with a ventricular pause, 1.7 seconds. After November 5 no further periods of bigeminy were noted. In one instance the character of the respiration during the tachycardia was not noted. During the hyperpnoeic periods the pulse usually showed an exaggeration of the irregularity.

Characters of the Paroxysmal Tachycardia.

These may be tabulated as follows (compare Fig. 10):—

No.	Onset.	Number of Beats.	Time Length of Paroxysm.	Pulse Frequency.	Offset.
1	Following two long pauses, interrupted by extra-systoles (Fig. 10 E).	23	10·7 sec.	129	Single beat 0·9 sec. length (Fig. 10 E).
2	Third beat before is ventricular pause 0·9 sec.; two beats just before paroxysm not measurable (Fig. 10 B).	20	11·0 sec.	109	Two immediately succeeding paroxysm not measurable, third beat is ventricular pause 0·9 sec. (Fig. 10 B).
3	?	more than 38	17·1 sec.	134	2 beats, each 1·05 sec. (Fig. 10 D).
4	?	33	13·2 sec.	150	2 beats, each 0·5 sec.; third beat, 0·85 sec. (Fig. 10 A).
5	One beat 0·80 sec.	59	29·5 sec.	120	Beat 1·2 sec. (Fig. 10 c).

The paroxysms of tachycardia are seen to be of variable duration and pulse frequency. The fastest rate was 150 per minute; the slowest, 109. The paroxysm of slowest frequency was ushered in by two prolonged pauses (ventricular), and the offset was also associated with a ventricular pause. The onset of the attack with the most rapid frequency was not gained, but its offset showed a resumption of the rhythm to its customary rate throughout the intervening periods, of about 70. The duration of the attack appears to bear no relation to the frequency of the pulse or the character of the onset or offset, both of which, in all the six instances (two onset, four offset), were abrupt. There was no exact doubling of the length of the cycle immediately succeeding the last cycle of the paroxysm. The character of tracings during the paroxysms shows that they cannot be of auricular origin, since the waves occur only 0·1 sec. before that of the radial, and must, therefore, be ascribed to ventricular activity.

It is also to be noted that the lengths of the cycles in the paroxysm are all shorter than that which separates the single or successive ventricular extra-systoles seen in other parts of the tracing, which were 0·65 second length, whereas in the tachycardias the length was never over 0·55 second. Such a length, however, is a close approximation to that which separates the wave in the tracing, Fig. 3. One more feature in the tracings was the frequency of ventricular pauses. Such were present in the apnoeic and hyperpnoeic periods. The longest pause was 1·85 seconds; in some places there was a succession of these pauses, thus, 1·5, 1·6, 1·75, 1·45; and again, 1·5, 1·6, 1·75, 1·45 seconds.

The patient remained in the same condition till November 9 (four days), when the attacks of more urgent dyspnoea gradually went. The digitalis was stopped on November 8. On November 8 the patient was rather drowsy, the
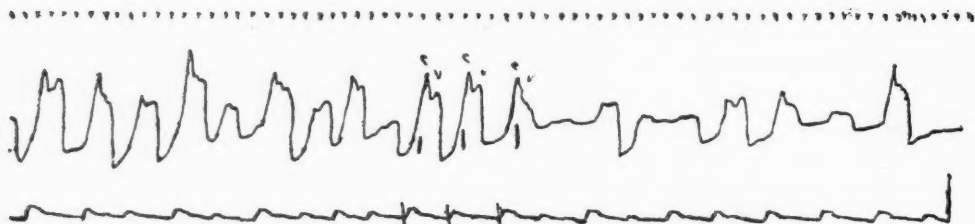
FIG. 5. Auricular fibrillation, Oct. 31, 1911. Pulse frequency 96.
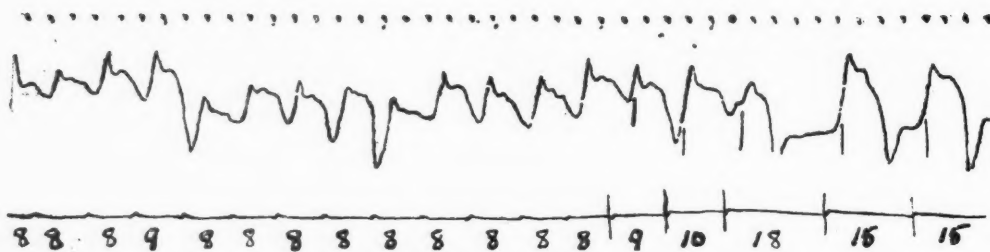
FIG. 6. Polygraphic curve, showing offset of tachycardia. Pulse frequency during attack, 130. Nov. 7, 1911.
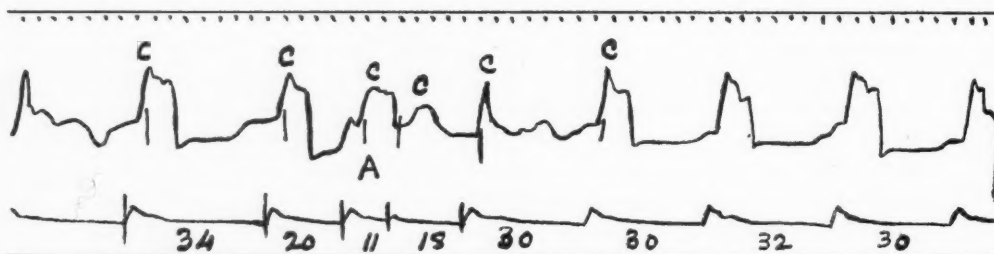
FIG. 7. High grade of *a–v* block, with occasional ventricular extra-systole, as at A. Ventricular rate 40. Nov. 10, 1911.
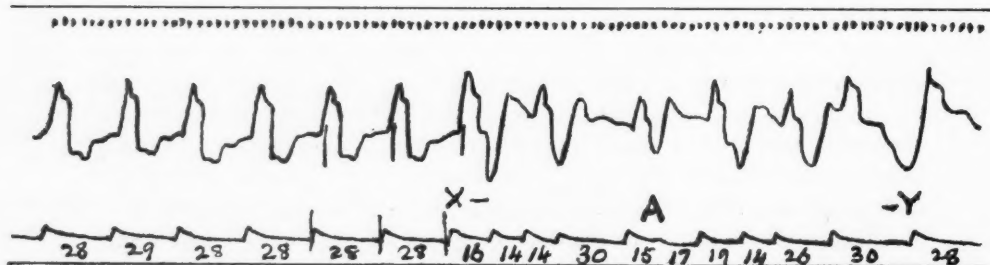
FIG. 8. High grade of *a–v* block, with occasional phases, X-Y, in which ventricular arrhythmia occurs. At A is a ventricular extra-systole. Nov. 10, 1911.

oedema had lessened, and there had been a well-marked diuresis. On November 9 the pulse was regular at frequency 40, and the tracing shown in Fig. 7 was gained.

The dominant rhythm throughout is a ventricular regular rhythm of frequency 40, or thereabouts. This rhythm, however, seems to be disturbed by what appear to be two different mechanisms. At A in Fig. 7 is seen an extra-systole, occurring 0·55 second after the previous normal systole. Several extra beats of identical character are seen elsewhere in the same tracing. These beats are, one considers, of similar character to those constituting the paroxysms. They may or may not be conducted to the radial. Their frequency and their irregular incidence cause the tracing to resemble in places that of ordinary auricular fibrillation, as at A in Fig. 8. In addition to these ectopic beats there are, in parts of the tracing, a loss of the regular ventricular beats and their replacement by a succession of beats of a slightly more rapid frequency : thus, in succession, beats of lengths 29, 33, 22, 21, 30, 31, and again, 30, 33, 31, 32, 19 ?, 15, 11, 34, 32—twentieths of seconds. The character of the wave shows them to be identical with those which accompany the ventricular beats of the regular cycles. One may infer from the tracing that there is an almost complete block at the junctional tissues; that the ventricle is beating throughout the greater part of the tracing with its own intrinsic rhythm; that this rhythm is occasionally disturbed by extra-systoles of a character similar to those which constituted the attacks of tachycardia ; and, finally, that in some places the con-ductivity is to a slight degree increased, so that some stimuli from the auricle reach the ventricle and this chamber responds in the usual irregular manner.

On November 13 the patient's general condition was unaltered. The drowsiness was still present. No dyspnoea. Some cough and expectoration. Slight pyrexia. Urine scanty and contains albumin. Breathing is of Cheyne-Stokes character. The pulse is of good volume. Heart-sounds as before. Tracings taken show that there is still a marked degree of a-v block. The character of the block, however, is different. It remains high for a certain period of time, and then it seems to be removed abruptly, and the ventricle begins to beat with a frequency almost double that of the preceding period. Such a change of frequency takes place within a few cycles, thus, 1·6 seconds (5 times), then 1·0 (6 times), then 0·8, 0·8, 0·8, 0·6, and so on in an irregular manner (Fig. 9). There is a marked difference in the size of the c waves in the venous tracing in the two phases, the waves being much larger in the slow periods than in the more rapid. There is complete absence of any ectopic beats similar to those seen on previous occasions. On November 15 the tracing shows a similar character, except that waves similar to those seen in Fig. 4 are again visible. On December 7 the patient's general condition was much worse ; there was an increase in the amount of the oedema ; there was some cyanosis ; and the tracing was typically that of auricular fibrillation, at frequency 90. Digitalis was withheld, though other forms of stimulant were freely administered. The patient got gradually worse, and died quite suddenly on December 22.

Post-mortem examination. Heart: The pericardium contains about an ounce of clear fluid. Myocardium appeared normal. Weight of heart, 32 ounces. In shape it was very rounded; of firm consistence. The walls of all the chambers of the heart were distinctly thickened; the cavities were dilated and full of agonal clot, but no thrombus. The valves were flaccid and there was a little opacity of the flaps of the mitral and aortic valves; no other abnormality. The aorta was markedly atheromatous throughout. There were patches, white and yellow, all over it. The coronaries were markedly atheromatous, as also were the splenic, mesenteric, iliac, and other arteries. Lungs: A few basal adhesions. Right lung more frothy than the left (patient used to lie mainly on his right side). The left pleural cavity contains about 10 ounces of clear fluid. Liver: 66 ounces weight, enlarged as a whole; of granular consistency throughout. Peritoneum: The cavity contained five pints of clear, straw-coloured, serous fluid. Spleen: weight 13 ounces, enlarged, firm, boat-shaped. Kidneys: Right—weight 6 ounces, bulky and firm. Capsule adherent,
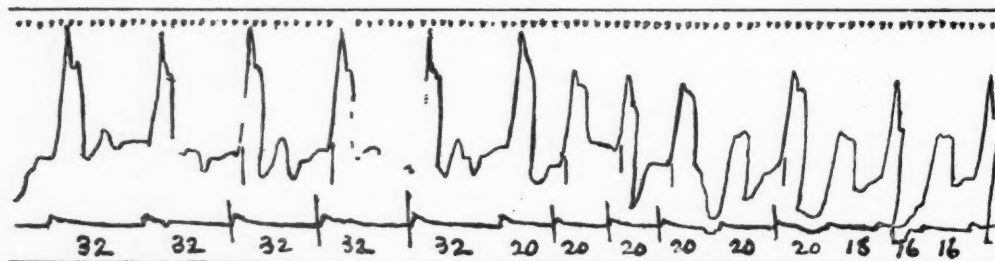
FIG. 9. Complete *a-v* block, with abrupt lapses into periods in which the ventricular rate is almost doubled, and the wave *c* lessened in size. Nov. 13, 1911.

surface irregular, granular, showing puckerings. The left kidney weighed 6 ounces, and was of similar character to the right.

Discussion. In the case under consideration the normal rhythm which dominates the ventricular response, namely the sinus, is absent throughout the whole period of observation, as the auricles are in a condition of fibrillation. Ventricular response is, in this case, the result of stimuli, received from three sources, (1) the irregular supraventricular stimuli received from the auricle, (2) the regular rhythmic ventricular beats (idioventricular), due to stimulus formation arising in the ventricle itself, and (3) rapid, regular, successive beats, in response to some focus or foci which generate stimulus material within the ventricle at a greater rate than the idioventricular activity. It is the changes and different combinations of such stimuli which induce the ventricular arrhythmia noted, and we would suggest, for reasons to be stated, that such changes arise largely as the result of alterations of the *a-v* conducting tissues induced by digitalis. The dominant ventricular rhythm for many months, in this case, was an irregular rhythm, directly induced by the auricular fibrillation. Throughout the whole observations this rhythm persisted. The ventricular

frequency associated with this rhythm was not high. On only one occasion was the pulse frequency counted over 110. On all occasions the giving of digitalis resulted in a slowing of the ventricular rate. The action of this drug upon the conducting tissues was marked, and all degrees of 'block' were noted, from a slowing with persistent arrhythmia, the 'bradycardial' type as noted by Mackenzie (2), to complete block (Fig. 9) associated with a ventricular regular intrinsic rhythm of frequency 40 or thereabouts. It is suggested that this direct sequence of events forms an important link in establishing the pathology of those cases of nodal bradycardia described by Mackenzie as being the result of auricular fibrillation associated with delayed a-v conductivity, for such a condition can in this case frequently be seen over prolonged periods, and then pass into a condition of complete block, the curves thus gained bearing a striking resemblance to those noted by Lewis (1), where the diagnosis of auricular fibrillation with complete heart-block was verified electro-cardiographically. The extent of the organic cause of the delayed conductivity in Lewis's case, however, was probably much greater than in this case, for whereas here the degree of block is largely dependent upon the digitalis, in the former case the degree of block was absolute throughout and unaffected by digitalis. In connexion with these differences were certain clinical distinctions. The onset of the block in this case was sudden and associated with subjective symptoms strongly resembling those of the Stokes-Adams syndrome (Oct. 26). Such an attack did not occur until the patient had taken, continuously over a period of eighteen days, 19·5 ounces of digitalis infusion, and 6 drachms of tincture of strophanthus. Again, the removal of the block occurred within a few hours of the stopping of the digitalis, with the resumption of the original arrhythmia. With the giving of digitalis there arose, first, frequent tachycardial attacks; secondly, periods of complete block, which passed gradually into partial block (Figs. 8 and 9) with the final stopping of the drug. It is of interest that the blocking was always of abrupt onset and equally abrupt offset, if one speaks in terms of successive cycles. The onset of the block which was induced on the second occasion was associated with a tachycardial attack to which I will presently refer.

We note, then, that the ventricular rhythm was influenced by the fibrillation of the auricle and the defective conductivity. It is probable that the auricles had been functionally inactive for a period of time exceeding two years. Such a condition, we know, is not uncommon, and may, as in this case, be compatible with a certain degree of physical activity. That such auricular disorder, however, played a large part in producing the final cardiac failure is probable. The character of the myocardium and valvular mechanisms was not such as is usually associated with pure myocardial degeneration. Nor could the degree of cardiac hypertrophy which obtained in this case have occurred had the heart muscle been previously damaged. We may consider this case, then, as one in which disturbance of rhythm was the dominant factor which led to the final dissolution of the patient. At what time or in what manner the auricles broke into fibrillation it is impossible to say. Nor is the direct exciting cause known.

Clinically and pathologically the case was one of chronic interstitial nephritis. There was, in intimate association with the renal changes, arterial degeneration
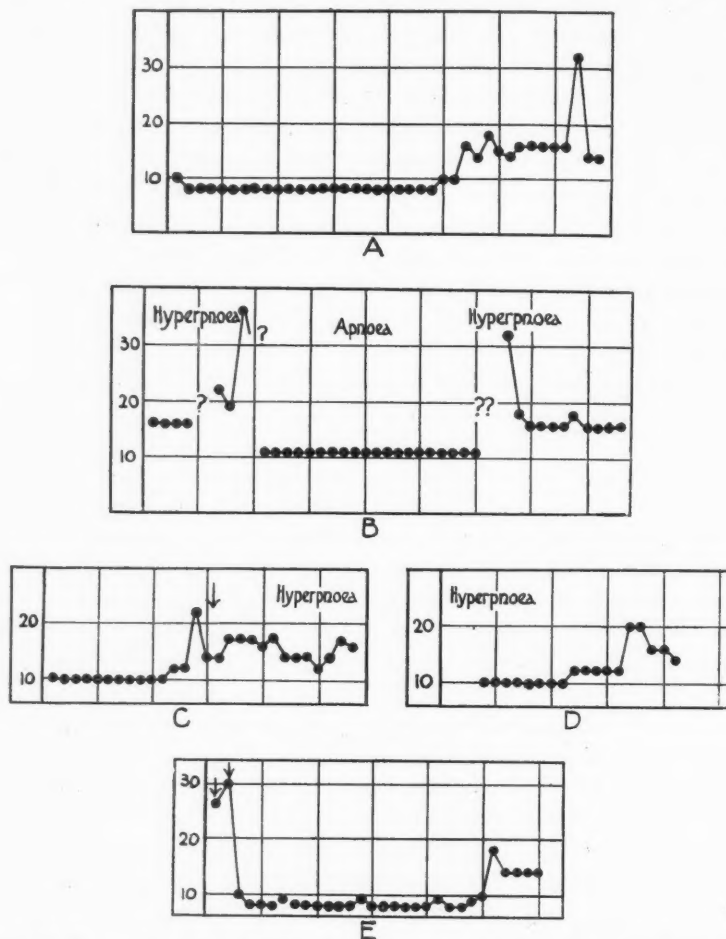
FIG. 10. Phases of tachycardia, occurring Nov. 5–7. Abscissae represent length of cycles in twentieths of seconds; ordinates, successive cycles. A C D and E show offset of tachycardia; B and E a complete period of tachycardia. Each dot represents a pulse-beat. The position of the dot in relation to the abscissa gives the length of time which intervenes between one beat and another; i.e. the length of the cycle. The beats follow each other consecutively. Thus in A we have one beat which occurs $\frac{10}{20}$ seconds after the preceding beat, next occurs a beat $\frac{9}{20}$ seconds long, and a series of 23 such beats of equal length follow (i.e. perfect regularity of rhythm). Such a frequency is 23 beats in 10·35 seconds, or 133 per minute. The length of the regular paroxysm (10·35 seconds) is succeeded by two longer beats, each $\frac{10}{20}$ seconds, then by a beat $\frac{16}{20}$ seconds, and so on. At the end of A is a single beat $\frac{32}{20}$ seconds long. The relation of the phases of tachycardia to hyperpnoeic and apnoeic periods will be noted.

of marked character, affecting the systemic and coronary arteries. The suggestion might be offered that such vascular degeneration change was, in part, responsible for the initial disturbance of cardiac rhythm.

There remain now to be considered the paroxysmal tachycardial periods. Accepting the view that, pathogenetically, tachycardias are analogous in every respect to premature beats, and own similar causes, it is possible that the tachycardia in the present instance may be due to a focus or foci initiating the heterogenetic rhythm in auricle, ventricle, or junctional tissues. That the present heterogenetic rhythm did not arise in the auricle is suggested by the fact that the auricle had been inactive as regards its power of co-ordinate contraction for a long period, and further by the fact that in the venous tracings of the paroxysms there is no evidence of a wave which could be attributed to auricular activity. The wave c in the tracing occurs $\frac{1}{10}$ sec. before the radial, but, were an auricular wave present, it would precede by a longer interval the radial wave.

In spite, then, of the greater frequency of auricular tachycardias, we hold that in this instance the source of the rhythm must be at some place other than the auricle. There remains to be considered the ventricle or the junctional tissues. It is a familiar fact that, preceding attacks of tachycardia, there may appear in the tracing single heterogenetic beats, whose source of origin is the same as that which initiates the successive beats which constitute the tachycardia. In this case we have frequent evidence that such single beats arise. As far back as January, 1911, the bigeminal character of the pulse is noted in the sphygmogram. The polygraphic curves taken at a later period also show similar premature beats of presumably ventricular origin. These occur either singly, as at A, Fig. 7, or successively in runs of considerable length, when associated with a frequency of slow character. In all instances, the time interval separating the premature beat from the preceding normal ventricular beat is identical, namely 0·65 sec. A difference, however, in this time period is noted in all premature beats which succeed the paroxysms. In these beats the time interval is shortened, and is only 0·4 or 0·55 sec., an interval identical, in fact, with that which separates the successive beats in the paroxysms. When one considers, then, whether the premature beats which preceded the paroxysms own a similar origin to those constituting the tachycardia, one is met with certain difficulties. Their frequency of incidence over the periods immediately preceding the tachycardia is much less ; none, in fact, were noted in any of the tracings taken over the three preceding days. Again, the time interval preceding the premature beat is considerably longer than that which separates the beats in the paroxysm, 0·65 sec., as compared to 0·4 or 0·55. Finally, the premature beats succeeding the paroxysms conform as regards time interval to those which constitute the tachycardia. No beats of a character resembling those which occurred before the paroxysm were noted. If it be accepted that the time interval of the premature beat from the preceding normal beat is identical from cycle to cycle, when it arises from the same source, we may infer that the source of the tachycardial beats is not identical with those responsible for the preceding ventricular extra-systoles, but is probably identical with those succeeding the paroxysm. Is the ventricle responsible for the single as well as the successive beats? In absence of electric curves it is, in our opinion,

impossible to say ; nor can it be determined whether, possibly, the nodal tissues are initiating the paroxysm. That the source of the paroxysm is situate at a higher level (functionally considered) than that which causes the single premature beats is suggested by the shorter time interval in the tachycardia. Were such the case, it seems reasonable to suppose that a drug, such as digitalis, which acts at the junctional tissues, in this case in particular would the more readily induce changes in a focus nearly related to the nodal tissues.

That the digitalis had an intimate association with the paroxysms is more than probable, but the exact means by which its activity could have been exerted can be only conjectured. We know that this drug can induce auricular tachycardia, and even fibrillation ; further, it is known to cause premature beats in the ventricle. But it is a far cry from single to successive heterogenetic beats, especially in the ventricle.

In connexion with the attacks of tachycardia must be noted the peculiar respiratory conditions. It was generally noted that it was when the dyspnoea was at its height that the heart broke into the tachycardia, and that this appeared to afford to the patient much relief from the distress accompanying the urgent hyperpnoea. Not on all occasions, however, was this close association noted. In other phases there was increased ventricular arrhythmia, or fairly prolonged ventricular pauses, more frequent in the apnoeic periods. From these facts it seems evident that nervous influences must have played a part in the production of the cardiac irregularities. In one instance, though the pulse was at frequency 76, the regularity was marked, and gave quite an opposite picture to what one usually sees in fibrillation, though there was still no evidence of auricular activity.

My thanks are here cordially tendered to Dr. Judson Bury for permission to publish details of this case, and to Professor Lorrain Smith for permission to record the result of the post-mortem examination.

Conclusion. A case is recorded of auricular fibrillation associated with a high degree of auriculo-ventricular block, and with attacks of paroxysmal tachycardia of (probably) ventricular origin.

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CONGENITAL OCCLUSION OF THE DUODENUM [1]

By E. MARSHALL COWELL

With Plate 19

Definition. By Congenital Occlusion of the Duodenum is meant a partial or complete interruption of the lumen of the bowel, usually situated in the vicinity of the opening of the bile duct. The occlusion may result from developmental errors or from antenatal disease.

Historical. The condition is somewhat rare. The earliest writing on the subject is by Aubéry in 1805. In 1812 Meckel quotes three fresh cases together with one case of his own. In 1837 Billiard, in his great work on children, describes a fresh case with a case described by Schäfer in 1824. In this year Rokitansky also fully describes a case of his own. Theremin, in 1877, writing on atresias of the alimentary canal, gives seven cases. He emphasizes the rarity of the condition: in 111,401 births there were two examples of the abnormality. In the lying-in hospitals of St. Petersburg 9 cases had occurred, but in Moscow and Prague the condition had never been found. Gaertner, in 1883, collected 16 cases and gives most of the literature up to date. Champneys, in 1897, showed a good specimen before the Pathological Society of London, but in his paper no extensive references are given.

The first recent paper which is at all comprehensive is by Cordes in 1901. He tabulates and analyses 57 cases with minute care. Kuliga, in 1903, collected 185 cases of stricture of the alimentary canal; in 59 of these the duodenum was affected. Operative treatment was mentioned by Ucke of St. Petersburg in 1907, but none of the latest papers have echoed his suggestion, and the operation of gastro-enterostomy has not yet been attempted. The papers mentioned are the chief ones on the subject; the most important are those by Cordes (57 cases) and Kuliga. At other times many observers have described isolated cases, so that now I have been able to collect 92 cases for analysis.

Clinical picture. This is best described by reference to the notes of a case recently observed.

The patient, a male child of 5¼ lb., was born on March 16, 1911, four weeks before full term. It seemed as well nourished as usual for its size. The parents were healthy; the mother had previously given birth to ten healthy children. Within two hours of its birth the child was vomiting vigorously. The

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[1] My best thanks are due to Dr. J. Poynton for permission to publish the case, and to Dr. Charles Bolton for many valuable suggestions.

vomit was dark in colour from the first and consisted of 'coffee grounds' material. There was never mucus ejected in any quantity. A few hours later the bowels were well open and a large meconium stool passed.

Haematemesis continued for fifty hours at gradually increasing intervals. The infant became weak and finally died 52 hours from birth. The motions were normal—contained no blood—normal urine was also passed, and beyond small feeds, which were immediately vomited, no treatment was adopted. On physical examination, the abdomen was distended in the upper part; no mass was felt. In this case peristalsis was not visible.

No definite diagnosis was arrived at. Purpura neonatorum was negatived on account of these facts : (1) Vomiting began two hours after birth. Thirty to forty hours is the common time for haematemesis neonatorum to commence. (2) Absence of bleeding from bowel and skin or mucous membranes.

Post-mortem. The abdomen was somewhat distended. When opened the greatly distended stomach immediately attracted attention. The stomach and first part of the duodenum were greatly dilated. The pylorus was easily distinguished by a groove. The stomach preserved its usual outline, while the dilated duodenum formed a globular sac which pressed upwards on to the gall-bladder. Just above the opening of the common bile duct the spherical distension ended abruptly in a narrow cord. Beyond this the rest of the duodenum continued in a perfectly normal fashion. The pancreas, liver, and spleen were normal. The remainder of the bowel was quite normal, containing meconium. The meconium presented the usual microscopical appearance, except that no hairs were seen.

The following measurements were taken after hardening. A list of measurements in a thirty-six weeks child of the same weight is given for comparison.

Stomach.

Length from cardia to pylorus (great curvature) . . .	16 cm.	Usual length 9 cm.
Maximum circumference . .	11·5 cm.	„ „ 7 cm.
Circumference of pylorus . .	4·5 cm.	·, „ 3·2 cm.

Duodenum.

Length from pylorus to occlusion (lower curvature) . . .	10·2 cm.	
Maximum circumference . .	11 cm.	
Circumference of occluded portion	9 cm.	
Circumference of second portion .	2 cm.	

On section the stomach and duodenum were distended with gas, but also contained about half a drachm of 'coffee grounds' material mixed with watery secretion. No bleeding-point was seen, but proper steps to find an ulcer were not taken. (The stomach was not opened and pinned out before hardening.) The first part of the duodenum ended in a little blind dimple. On dissection the common bile duct was seen opening coincidently with the pancreatic duct a short distance below the stricture. Two longitudinal folds of mucous membrane ran up the posterior wall of the duodenum. They increased in size and gradually diverged as they reached the neighbourhood of the bile papilla. At this point each fold became very marked and turned sharply outwards to meet the lateral walls of the duodenum. The folds presented free edges; arching outwards they practically met beneath the anterior wall, but left a small tunnel on the posterior wall. This led into a space which rapidly narrowed until the bowel was no longer pervious. A small fold in this space contained the opening of the bile duct. Section of this portion showed the whole diameter much diminished

and muscular walls increasing in thickness as the lumen diminished till the whole formed a small solid rod.

Length of strictured portion	. .	1·1 cm.
Length of solid cord . .	. .	0·5 cm.
Circumference . . .	. .	0·9 cm.

Analysis of Recorded Cases.

Cordes has made a careful analysis of the collected cases of his series. The results of the additional 35 cases are given below.

Sex. My figures show 8 male and 8 female, the sex is not mentioned in 19. In the whole series there are 21 males, 22 females, and 49 doubtful cases.

Frequency and nature of vomit.

	Cordes's cases.	Fresh series collected.	Total.
Vomiting present	41	13	54
Not recorded	16	22	38
Blood, old or recent	27	7	34
Bile	2	2	4
Food	2	—	2
? Nature	10	4	14

Position of occlusion.

	Cordes.	Fresh series.	Total.
Above opening of common duct	20	11	31
Below opening	13	7	20
Level with	6	3	9
Not mentioned	18	14	32

Presence of other abnormalities in the alimentary canal.

None beside duodenal occlusion	54 cases.
Stenosis of other parts of bowel	8 cases.
Foetal peritonitis	3 cases.
Enlarged liver and spleen	1 case.

Pathology.

Position of occlusion. In the table prepared from the study of all the recorded cases the situation is accurately mentioned in 60. The common bile duct opens above in 31 cases, below in 20, and on a level with the occlusion in 20 cases. The Vaterian segment is the commonest portion of the duodenum affected. One would have expected this result, since this is the situation of so many important embryological events. Here the liver and pancreatic buds grow out, the lumen is at one time occluded, and the morphological fore-gut becomes the mid-gut.

Date at which occlusion occurs. In discussing the source of the stricture we shall see that certain changes occur before the second month of intra-uterine life which greatly help in the explanation of the formation of this condition. In a large number of cases in which the septum is below the common bile duct normal meconium is present in the bowel. This shows that the stricture was formed after the third month, when bile begins to be formed. In the present case the occluded portion measured 0·9 cm. in circumference, while the rest of the duodenum was 2 cm. There was no evidence of any gross disease having caused the difference in size. Supposing at this point this portion of duodenum ceased to grow, then by comparison with other foetuses we should be able to time the occlusion. Unfortunately I have not been able to obtain such data at present.

Source of the occlusion. There are two possible methods by which such an occlusion may arise: (1) By an error of development; (2) As the result of definite antenatal pathological processes. In the majority of cases no actual cause can be discovered, and an explanation is sought by means of developmental theories. Tandler has very carefully studied the development of the Vaterian segment of the duodenum in embryos of from thirty to sixty days. In his series the lumen of the gut is clear in the youngest and oldest embryos, but in the intermediate stages becomes blocked by a cellular proliferation. It is easy to see how a complete or partial failure of this plug to absorb can account for any grade of occlusion. The difficulty, if we accept this view of the patho-genesis of the condition, is to reconcile the dates of this cellular proliferation and the excretion of bile. In a small proportion of the cases a definite cause for the condition can be assigned.

Foetal volvulus. At one time this was the favourite explanation of the occlusion. Kutner (1857), in considering his case, dismisses volvulus and says there is no evidence for this explanation. Rokitansky, Schottelius, and Gaertner all quote cases, but the evidence is poor. Kuliga (1903) says that in one or two of the undoubted volvulus cases, the volvulus is the result and not the cause of the occlusion. Gross (1905) describes a very interesting case of a newborn infant with a mesoduodenum. The rotation of this portion of the bowel had not occurred, and the duodenum hung as a movable loop, so that no attempt at volvulus, however, was present. Claremont (1905) found in an adult a duodenum completely twisted on itself, but no obstruction was present.

Foetal peritonitis. Cases where the occlusion has undoubtedly been due to adhesions in foetal peritonitis are quoted by Theremin, Hirschsprung, v. Dohrn, Fielder, and Gaertner. Silbermann, in his study of foetal peritonitis, however, finds that it is very rare to see an associated stenosis of the bowel. Volvulus is sometimes associated with this condition; cases are described by Fielder, Wieder-hofer, Schottelius, and Mauclaire.

Rarer causes of occlusion of the duodenum. These causes are so rare that they become merely pathological curiosities. Wyss and Hammer have described hypertrophy of valvulae conniventes causing obstruction. Baillie, in

1827, wrote of a case where he found in an adult a very large valvula connivens almost occluding the bowel. Hess met with a case apparently due to compression by the mesocolon. Nobiling found the bowel strangulated by a loop of the omphalo-mesenteric artery. Schott and Wünsche respectively found a cyst in the iliac fossa and an inguinal hernia pulling on the mesentery. Hirschsprung and Sever found cases where the head of the pancreas seemed press on the bowel. Wiederhofer described an antenatal carcinoma of the liver, and Kristella a large liver pressing on the bowel.

Why does the stomach dilate? The dilatation of parts above the stricture is generally a marked feature of the case. The pylorus becomes marked as a groove. Some of the earlier authors failed to recognize this fact, and spoke of a bilocular stomach. In cases where the condition is found in stillborn infants the stomach is full of mucus or watery fluid, while in the cases born alive large quantities of fluid are usually vomited from the very first. The presence of this fluid is probably the cause of the dilatation. The mucosa-lined muscular sac secretes fluid under pressure and dilates in just the same way as does a gall-bladder with obstructed duct. The dilated stomach may in fact be looked upon as a mucocele.

Source of the bleeding. Haematemesis occurs in about 65 per cent. of the collected cases. The exact cause of the bleeding, however, is not clear. In my case the presence of an ulcer cannot be absolutely excluded, since the stomach was not opened and pinned out at once after death. In the case of Schütz a tiny erosion was actually discovered and the opening into the vessel was found plugged with a recent clot. The entire portal system appears to be congested in a good many of the cases. In the photograph shown the vessels stand out clearly. No bleeding occurred from the mucosa below the stricture, however, while the dilated portion above was full of blood, so that simple portal congestion will not account for the bleeding. In the majority of cases there is haematemesis from the first. Occasionally, however, mucus is first vomited, and only later as the vomiting continues does blood appear. In the case of Funck-Brentano, the child vomited mucus, then material streaked with blood, and finally large quantities of blood. The conclusion is, therefore, that in most of these cases the gastrorrhagia is mechanical in origin, resulting from the strain of vomiting on an already over-distended stomach.

Diagnosis.

The points on which a diagnosis can be made are quite definite. *Vomiting.* In all the cases where vomiting is mentioned at all it is recorded as being present, so that in fifty-four cases vomiting was present; the point is not mentioned in thirty-eight. The vomiting usually begins at once after birth; the material is forcibly ejected and is got rid of in large quantities. *Haematemesis* occurs in about 65 per cent. of the cases. The bleeding differs from that of purpura neonatorum in that it usually comes on almost at once after birth, and is not

accompanied by melaena or other evidence of purpura. Although the vomiting is persistent and severe, yet usually the bowels are well open and normal meconium is passed. In occlusions of the bowel lower down constipation is usually absolute. *Of physical signs.* The upper abdomen is distended; sometimes peristalsis may be seen. Cyanosis is usually present, since the diaphragmatic action is so impeded. Bismuth given for X-ray diagnosis has not yet been tried, but should prove a useful aid in these cases.

Treatment.

The condition has been so little recognized that but scanty opportunity for treatment has arisen. In the few cases where a diagnosis has been made, lavage has been tried. Five cases have been subjected to laparotomy, those of Wyss, Simmonds, Hess, Kirmisson, and Schütz. Enterostomy has been attempted in each of these cases, but in none has the infant survived more than a few hours. Ucke of St. Petersburg, in 1907, suggested gastro-enterostomy, but this has not yet been carried out. As far back as 1899 Abel performed a successful gastro-enterostomy on an eight-weeks-old infant for hypertrophic pyloric stenosis (the time of operation was forty minutes). So that with the present-day improvements in technique this operation should be at least considered justifiable to attempt. In more than half the cases available for analysis the opening of the common bile duct was below the stricture, so that in a gastro-enterostomy there is not a great risk of trouble from this source. In about ten per cent. of the cases some other deformity exists, as multiple stenosis of small intestine, absence of anus, and so on. In these cases the clinical picture characteristic of occlusion of the duodenum, vomiting normal action of the bowel, does not obtain. The infants live a variable time with complete occlusion. Death usually takes place on the fourth or fifth day. The longest life is nine months (quoted by Keith). With partial stenosis one case lived as long as eighteen months (Buchannan). From the consideration of these facts it would seem that the cases should be subjected to laparotomy, and if possible gastro-enterostomy should then be performed.

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DESCRIPTION OF FIGURES.

FIG. 1.   View from the front, showing dilated stomach and duodenum.

FIG. 2.   Tracing from photograph of anterior view of viscera.   The size of a normal stomach and duodenum is represented by the dotted line.

FIG. 3.   View from behind entrance of bile and pancreatic ducts just below occlusion. D^i. First portion of duodenum. D^{ii}. Second portion of duodenum.   Between these two parts is seen the bile duct B opening just beyond the stricture.

FIG. 4.   Diagram of site of atresia magnified about three times.   (*a*) First portion of duodenum in blind pit.   (*b*) Cord-like portion above opening of common bile duct.   (*c*) Normal second portion, with longitudinal folds.   (*d*) Common opening of bile and pancreatic ducts.

FIG. 5.   Diagrammatic sections taken from below upwards (× 3).   I. The two folds. II. Turning outwards before reaching the bile duct.   III. The bile duct.   IV. Just above bile duct.

FIG. 3
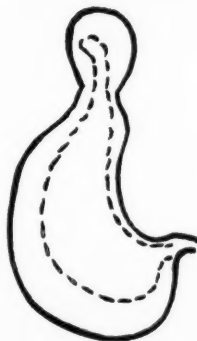
FIG. 5

FIG. 2
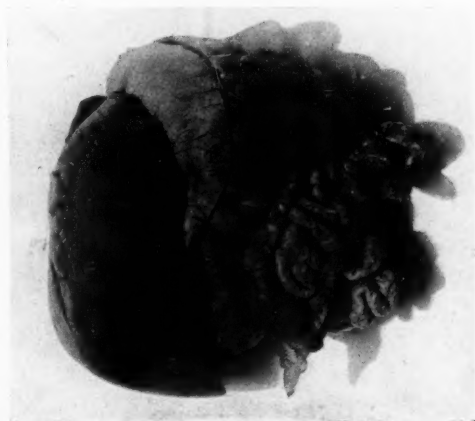
FIG. 1
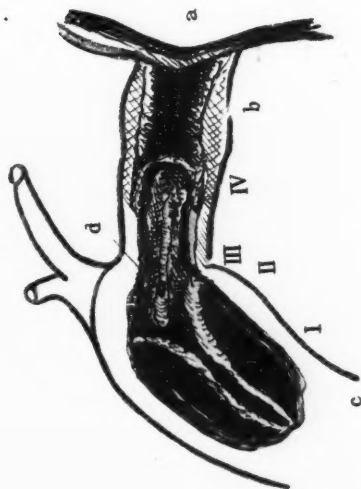
FIG. 4
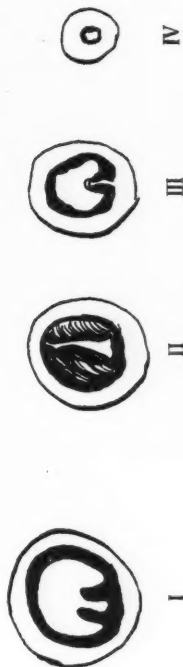
CONGENITAL ATRESIA OF THE BILE PASSAGES

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With Plates 20 and 21

THE frequent occurrence of jaundice in the new-born and the wide scope of possibility of its etiology render it one of the most important conditions of childhood. In this disease there is, however, one group, perhaps the least common, where the symptoms and pathological signs are more definite and where the process seems to depend on some defect of the bile passages.

This condition has been noted from time to time in medical literature, but to John Thomson in 1892 belongs the credit of first accurately describing and systematizing the disease. It is perhaps more common than is usually supposed, yet only some seventy-eight cases are recorded. This number, however, only includes those which have been sufficiently described to be conclusive, and excludes numerous cases, such as those of Hochsinger, Lavenson, &c., where the pathological evidence was incomplete, and also those where the process may have been due to syphilis, gall-stones, hereditary family jaundice with normal bile ducts, or even acute liver atrophy or cirrhosis.

It still presents certain unsettled questions and is of sufficiently rare occurrence to allow of the publication of another case.

The present case occurred in a male child who was admitted to the ward of Dr. John Thomson in the Sick Children's Hospital, Edinburgh. The child was the first-born of healthy parents in whom there was no tuberculous or syphilitic history. The father, however, stated that two of his brothers had died in infancy from jaundice, one at the age of ten days and the other at three months.

The pregnancy was uneventful. The child was born at full term by a natural labour and looked very healthy at birth. It was fed on the breast and took food very well. There was a slight tendency to constipation and occasional attacks of vomiting, but no diarrhoea. The condition of the meconium had not been noted. The stools were pale and their odour very offensive.

A week after birth the child was noted to be yellowish all over. This colouring increased and had been persistent ever since, with periods of more marked intensity. The motions were pale in colour and scanty and were passed about eight or nine times daily. There was no more vomiting than in a healthy child. The urine was noted as highly coloured.

The child first came under observation at ten days old. It slept normally, took the breast regularly, and continued thriving. On examination at ten weeks old it weighed 10 lb. 7 oz., and appeared very well nourished. There were no external congenital anomalies, with the exception of a small umbilical hernia.

[Q. J. M., July, 1912.] G g

The skin, sclerotics, tongue, and gums were deeply jaundiced. The head was natural in shape, 15¾ inches in circumference, the anterior fontanelle patent and of normal tension. Nothing abnormal was noted about the eyes, nose, or ears. The thorax was well formed, 16 inches in circumference. The abdomen was prominent, 16 inches in circumference, and showed a small umbilical hernia. There was no local tenderness in the abdomen and no palpable lymphatic glands. The respirations were 24, pulse 116, and the temperature 98°. The urine contained a large amount of bile pigment. The stools were loose, pale, and slightly green in colour, and contained a good deal of mucus.

The liver was found 2½ inches below the costal margin in the right nipple line, extending down to the level of the umbilicus. Its lower edge was smooth and firm. The gall-bladder was not palpable. The spleen could be felt two finger-breadths below the left costal margin.

The respiratory and circulatory systems showed no special change. The condition remained about the same, nutrition remaining fairly good, until death occurred suddenly at fifteen weeks old, from haematemesis.

At the autopsy in this case all the organs were found to be deeply jaundiced, but otherwise no important change was found in the heart, lungs, blood-vessels, kidneys, suprarenals, or brain. The intestines were somewhat distended and somewhat congested. There was no ascites. The spleen was considerably enlarged, firm, and on section darkly congested. On microscopic examination there was found to be, besides stasis, a moderate degree of hyperplasia of the *intersinus* cells and also some hyperplasia and desquamation of the lining endothelium cells.

The pancreas appeared normal to the naked eye, but on microscopic examination there was a slight increase in thickness of the interlobular connective tissue, but no evidences of recent inflammatory connective tissue. There was no interacinous inflammatory change. The pancreatic duct opened normally into the duodenum. It was pervious throughout and did not in any part seem dilated.

The common bile duct could not be found in any part of its course below the junction of the cystic and hepatic ducts. The gall-bladder was markedly dilated. The cystic and hepatic ducts were well formed and also considerably dilated. There were no evidences of peritonitis and no abnormal adhesions were found in any part of the abdominal cavity. The liver was enlarged considerably and of a deep green colour. Its surface was finely granular, and on section a narrow zone of connective tissue could be seen surrounding the liver lobules. Microscopically a considerable degree of cirrhosis was found. As is seen in Fig. 1, a comparatively wide zone of young connective tissue occupied the outer part of the lobules. Through this fibrous tissue ramified many ducts. These ducts were for the most part branching and in direct communication with liver-cell trabeculae and interlobular bile ducts. They appeared as if they were the normal bile-conducting channels situated in an inflammatory environment denuded of liver cells, and whose lining epithelium had been transformed into a cubical type.

The interlobular bile ducts were slightly dilated, but were not specially catarrhal, nor did they show any inflammatory organization in their interior.

This case corresponds in type to the majority of those previously recorded. The clinical records of these cases show that the parents have generally been healthy and pregnancy has been uneventful. Labour, so far as has been noted, has been only rarely abnormal. More boys have apparently been affected than girls. In thirty-four cases quoted by Thomson, twenty-one were boys. In several instances there was a large family of healthy children before the patient

FIG. 2.   Weigert stain.   Twelfth dorsal segment.   Degeneration in posterior column and in the lateral column.
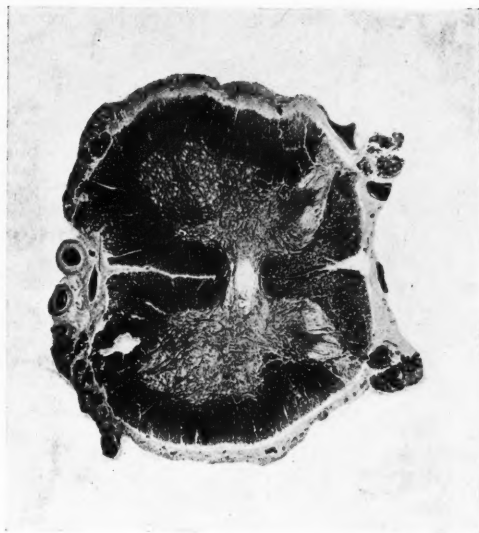
FIG. 4.   Weigert stain.   Fourth sacral segment.   Posterior and lateral column degeneration.

FIG. 1.   Weigert stain.   Degenerations in the posterior root zone. Third lumbar segment.
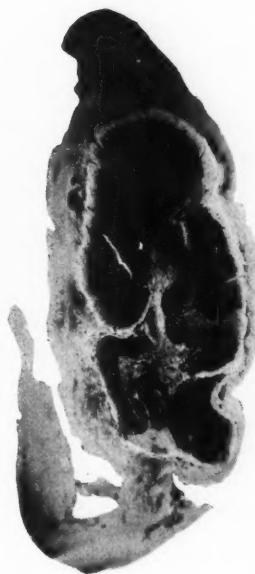
FIG. 3.   Weigert stain.   Degeneration in posterior column. Distortion of the cord and extensive meningitis.   Sixth cervical segment.

Fig. 5. Haematoxylin stain. Intense meningitis.
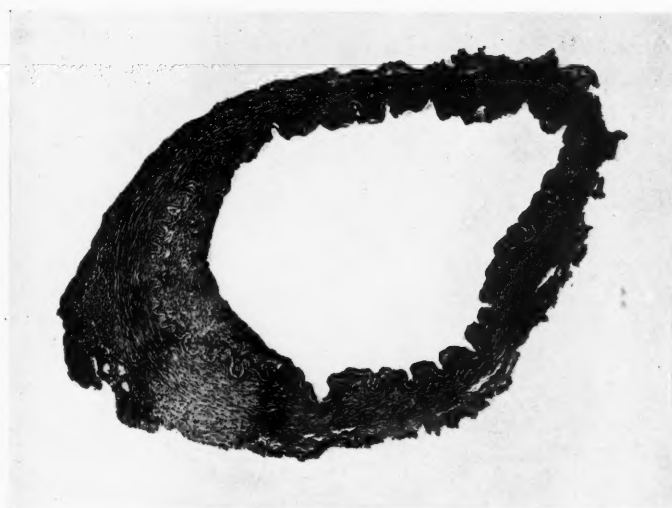
Fig. 6. Endarteritus. Branch of the basilar artery.

was born, and generally also it was the only one affected. It is interesting to find, however, that the records of a considerable number of the cases show that jaundice was recurrent in succeeding members of the family. Glaister, for instance, reports a family where four infants died jaundiced and two others were born jaundiced but recovered. In Thomas's report also, four previous children had died jaundiced. In only one instance, that of Binz, so far as I know, has an autopsy revealed more than one member of a family to have had an atresia of the bile passages. Considering this fact, and that in many cases of what has been termed recurrent familial jaundice autopsies have shown normal bile passages, it is doubtful if many of the cases where the disease was reported as recurrent were genuinely due to atresia of the bile ducts.

The *symptoms* in most of the cases have been fairly uniform. Jaundice is noted at birth or occurs shortly afterwards. In seventy-eight cases, thirty-nine were born jaundiced. In Glaister's case jaundice came on just after birth ; in those reported by Murchison, 1 day ; Donop, Cnopf II, 2 days ; Stooss I, Cnopf I, Binz III, and Hébert, 3 days ; Fuss and Boye, 4 days ; Giese and Hawkins, 8 days ; Morgan and Thomson, 10 days ; Wilks and Westermann II, 14 days ; Parker, 3 weeks, and Skormin, 5 weeks after birth. The jaundice at first may be very faint, but sooner or later becomes very intense, and bile in the urine has been observed in practically every case.

The meconium has been noted as normally coloured in eight cases, and in six it was devoid of its normal bile colouring.

The description of the motions has also varied, although in the great majority of instances there has been no bile staining from the beginning. Thomson has considered the colouring of the faeces in his case as possibly due to the activity of certain green colour-producing organisms in the intestine. As Giese says, however, it is possible that in any jaundice case bile may exude through the intestinal wall and colour the contents.

It is characteristic that the general nutrition in almost every case was well preserved till near the end. Death usually occurs about the fourth month, but has been recorded at all ages between sixty-two hours (Glaister) and eight months (Lotze).

The present case terminated by haematemesis. There seems indeed to be some special tendency to haemorrhage. In 49 cases collected by Thomson there were 32 which showed this (subcutaneous 7, subconjunctival 1, umbilical 6, nasal 2, haemoptysis 1, haematemesis 4, from the bowel 8, from the mouth 1, into the gall-bladder 1, excessive bleeding from a leech-bite 1). This, however, does not seem due to any special peculiarity other than pertains to the jaundice. In this connexion the work of Ribadeau has some relation, as he showed that following the ligature of the bile duct in guinea-pigs a remarkable degree of anaemia was produced. Anaemia may thus also be a factor responsible for the haemorrhages which so commonly occur in these cases.

The *pathology* of this disease is particularly interesting and presents considerable individual variations. The essential lesion is some defect of the

biliary passages, the surprising variations in type, location, and extent of which the following table gives some indication :—

I. *Common Bile Duct.*

Impervious or absent	70 cases

(In 5 only was the duodenal end of the bile duct pervious.)

Absent	34
Absent except 1 cm. at duodenal end	1
Replaced by a fibrous cord	7
Obliterated	8
Obliterated and embedded in fibrous tissue . . .	4
Lower half obliterated	3
Lower half obliterated in fibrous tissue	3
Obliterated at duodenal end	1
Obliterated at duodenal end by fibrous tissue . . .	2
Absent at duodenal end	5
Obliterated in fibrous tissue at its upper end . . .	1
Only small portion left midway	1
	— 70

In these 70 cases *common hepatic duct* absent . .	23
„ „ „ . „ „ obliterated .	16
	— 39

Common hepatic duct absent or obliterated and *right and left hepatic ducts* both absent . . .	3
„ „ „ obliterated	4
	— 7

Common hepatic and cystic ducts both absent . . .	15
„ „ „ „ obliterated .	11
„ hepatic duct obliterated, cystic duct absent .	1
„ „ „ absent, cystic duct obliterated .	4
	— 31

Gall-bladder present with no cystic duct	7
„ rudimentary with no cystic duct . . .	2
Gall-bladder and cystic duct present with no common bile duct and no hepatics	3
Gall-bladder and cystic duct absent	1

II. Common hepatic and right and left hepatic ducts impervious or absent	6
III. Hepatic and cystic ducts impervious	2

Besides these cases where the direct course of the bile excretion has been obstructed, other anomalies of the bile passages have been reported :

IV. Gall-bladder and cystic ducts absent	3
V. Gall-bladder absent	3
VI. Gall-bladder rudimentary and cystic duct absent . . .	1
VII. Gall-bladder rudimentary and cystic duct narrowed . .	1
VIII. Cystic duct obliterated	4

The liver in practically every case has been reported as enlarged, and where it has been examined microscopically has shown a similar characteristic picture to what was observed in the present case. The degree of cirrhosis is largely dependent on the duration of life, and where death occurred early, as in Griffith's case, aged 10 days, there was little or no inflammatory change in the liver. It has commonly been noted as a biliary cirrhosis. Rolleston and Hayne

described it as 'mixed, partly multilobular; that is, ordinary portal cirrhosis from the effects of poisons entering by the portal vein; and partly monolobular, the effects of poisons entering by the branches of the hepatic artery'. In this connexion, however, it must be remembered that the radicles of the portal vein and hepatic artery anastomose in the portal spaces, so that any poison which enters the liver by these two channels must affect the same situation. Mono-lobular cirrhosis is that condition where the peripheral portion of the liver lobule has been surrounded or, as is more usual, replaced by connective tissue. The term 'multilobular' is not strictly correct, but the variety of cirrhosis which goes by this name is produced as the result of a continued or frequently repeated destruction of small portions of liver tissue, at first starting like the mono-lobular variety but, continuing, causing irregular destruction and necessitating extensive liver-cell regeneration. These two processes of irregular destruction and regeneration in turn produce an extremely irregular outline of the masses of liver cells included amongst the scar tissue. The so-called mixed type of monolobular and multilobular cirrhosis which Thomson, Rolleston, and others have described is, then, simply an advanced stage of the monolobular variety where the destruction, cicatricial repair, and liver-cell regeneration have more or less extensively altered the normal lobular structure of the liver.

In several cases the pancreas has been described as cirrhotic. Some of these are undoubtedly genuine. Yet others are only descriptions of the normal pancreas, which in the newly-born always has the appearance of containing more fibrous tissue than in the adult.

The spleen has generally been described as enlarged. In one case (Emanuel) it has been noted as fibrosed, but from the description it is uncertain whether it was the result of infarction, haemorrhage, or merely the thickening of the trabeculae consequent on advanced venous stasis. As a secondary event to the liver cirrhosis it is natural that the spleen should be enlarged both by stasis and by reactive changes induced by circulating toxic substances which the liver is unable to eliminate.

The glands at the root of the liver are as a rule enlarged, but this is natural when one considers that in such cases bile must be extensively passed into the lymphatics leading from the liver.

With these few exceptions no other distinctive pathological lesions are found. Chronic peritonitis or any inflammatory change round the larger bile ducts which might have caused the obstruction has only rarely been observed.

Evidences of syphilis in particular have been conspicuously wanting. In twenty-three out of eighty-nine cases of atresia of the bile passages syphilis was absolutely excluded both as regards the parents and the child. In only ten cases there was reported some manifestation of syphilis or else a syphilitic history in the parents. In all of these, however, the evidence that syphilis was the cause of the atresia and the liver condition is insufficient. In Cnopf's case, for instance, he assumed undoubted lues from the finding of a liver cirrhosis with round-celled infiltration, but similar appearances may be noted in any

case of cirrhosis. Skormin similarly diagnosed syphilis from scar tissue in the portal spaces.

Syphilis does, however, produce well-marked changes in the liver and bile ducts. It causes a form of cirrhosis of a characteristic intercellular type, very different from the monolobular or biliary variety found in cases of primary bile-duct atresia.   In congenital syphilis there is occasionally a very extensive infiltration of the bile ducts which may be sufficient to cause complete obliteration. Cases of this sort have been well illustrated by Rolleston, Chiari, Beck, Hansemann, and others. I think also that the two cases of Schüppel, and those of Simmoni, Hutinel and Hudelo, and Lomer, although described as congenital obliteration of the bile ducts, were essentially syphilitic in type.

Rolleston and others, although denying any etiological relationship of syphilis to this group of cases, advocate that the process of atresia of the bile ducts is the result of a cholangitis occurring in early foetal life which finally leads to obliteration. They assume some toxic process in the mother or the child which in course of elimination by the liver causes a cholangitis. Undoubtedly poisons circulating in the child may be eliminated by the liver and might cause a cholangitis. Undoubtedly also it would require only a very small amount of damage in early foetal life to produce very extensive lesions as the biliary system developed. Against this, however, must be reckoned the well-established fact of the good health of the mother during pregnancy in such cases, and the well-nourished state of the child at birth. Even though some toxic condition did exist in the mother, the child has a remarkable protection, as even jaundiced women do not have jaundiced children. It is also rare to find lesions in the child which might be considered as a source of infection, and the atresia of the bile passages found at autopsy, even in cases dying shortly after birth, is fully developed. No early cases seem to have been noted. According to Rolleston's idea the liver ought to be uniformly involved, yet the degree of cirrhosis seems to depend largely on the duration of the child's life.

In those cases where death has occurred early, as in Griffith's case, the liver was relatively slightly affected. It would also be peculiar if a toxic process, even if of some specially rare type, caused an obliterative cholangitis at any one period of foetal life, and also, if this were the cause, atresia ought to be of much more frequent occurrence. In addition, it is difficult to understand how any inflammatory process could produce a total absence of the bile passages, as is so commonly found in these cases. Much more difficult is it to explain in this way such conditions as total absence of the gall-bladder and bile duct, absence of the cystic duct with a persistent gall-bladder, and obliteration of the cystic duct alone.

The liver in the present case showed no marked signs of cholangitis and there was no obliteration of the smaller ducts. The cirrhosis might, of course, have been produced by any damaging agent arriving by the portal vein or hepatic artery. Similar appearances, however, can equally readily be the result of gall stasis following some obstruction of the bile passages.

Occlusion of the bile duct by stone, even in adults, and experimental ligature of the duct in animals does produce a considerable degree of cirrhosis. Fig. 2 represents the liver of one of a series of twelve cats, in each of which the bile duct was ligatured. All these cats, with the exception of one which succumbed on the fifth day, died in a very emaciated state between the third and sixth weeks after the operation. In all of them the liver showed a considerable degree of cirrhosis. The bile ducts above the ligature were enormously distended. In the liver, however, the smaller ducts were commonly observed to be in a condition of cholangitis, and frequently also they were almost completely obliterated by fibrous tissue (Fig. 3). The portion below the ligature was reduced in size but not obliterated by fibrous tissue, and certainly in no case had disappeared entirely.

Foetal cholangitis in relation to the production of atresia of the bile ducts has been generally considered as descending, yet certain authors have considered it as spreading from the duodenum. Inflammatory lesions in the duodenum of any sort, even syphilitic, are, however, so rarely found in foetal life that this mode of infection may practically be discarded.

Summarizing the facts, both clinical and pathological, it seems as if almost every evidence indicates some congenital malformation as the cause of this group of cases of jaundice in the newly-born. In only very few cases, however, has the lesion been associated with other congenital deformities. (The cases of Witzel, Wünsche, Simpson, and Hébert were examples where multiple deformities did coexist.)

Several authors have attempted to explain the exact cause of this defect, and in this direction only theories can be formed. Legg and Skormin considered that the bile duct simply was never formed. The liver is developed primarily from a groove in the surface of the duodenum, which deepens, and on its summit the liver ' Anlage ' develops. As the primitive liver enlarges and separates from the duodenum, the depression on which it is situated is drawn out as the primitive bile duct. In the same way the gall-bladder develops from the bile duct. The liver, therefore, cannot develop without the bile duct. Beneke has accounted for the defect by supposing there has been some discrepancy in the normal balance of growth between different tissues differentiating adjacent to one another. Most congenital defects, as he has shown, take place in situations of cleavage where cell-groups are differentiating. Oesophageal stricture, for instance, generally occurs where the lungs separate off. In relation to bile-duct atresia, he thinks it is due to a lack of normal relative balance in growth of the duodenal tissues, which prevents the proper development of the bile duct. ('. . . als ein Ausdruck eben der gesteigerten Wachstumsdifferenz, der inneren Entfremdung zwischen Gallengangs- und Duodenalepithel anzusehen ist.') This does not seem to account for those cases of atresia where only a portion of the biliary system is defective, nor for such anomalies as the absence of the gall-bladder or cystic duct. If an opinion is necessary in this connexion it seems more probable that the cells composing the primitive bile duct in part or altogether fail to differentiate and form the fully-developed structure.

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EXPLANATION OF FIGURES.

PLATE 20, FIG. 1.   Section of the liver showing a condition of monolobular cirrhosis.   A wide area of young fibrous tissue, containing numerous bile ducts, surrounds the liver lobules.

FIG. 2.   Section of the liver of a cat, showing a considerable increase in the fibrous tissues of the portal spaces.   The animal died five weeks after ligature of the common bile duct.

PLATE 21, FIG. 3.   Section of the liver of a cat that had died six weeks after ligature of the common bile duct, showing almost complete fibrous obliteration of an intrahepatic bile duct.
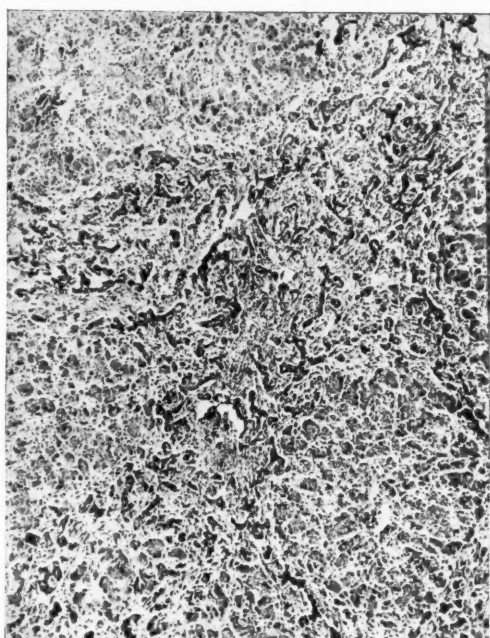
Fig. 1
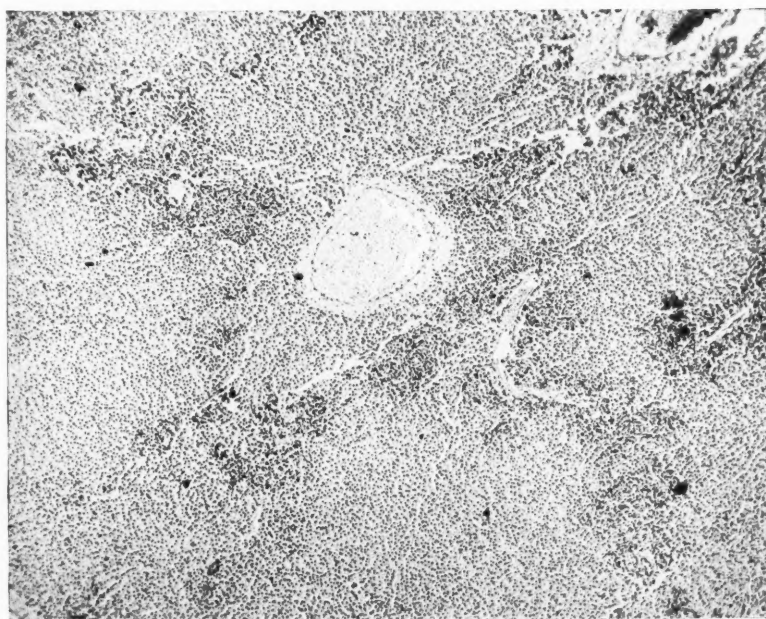
Fig. 2

FIG. 3

THE ACIDOSIS INDEX

A CLINICAL MEASURE OF THE QUANTITY OF ACETONE BODIES EXCRETED IN THE URINE

By T. STUART HART

THE condition of 'acidosis' due to the production in the organism of the acetone bodies in abnormal quantities is to-day of great clinical interest. It is met with in a large number of conditions (1), among which may be mentioned starvation, the sudden withdrawal of all carbohydrate food, certain digestive disturbances such as cyclic vomiting, &c., some febrile diseases, after anaesthesia, and notably in diabetes mellitus in its advanced stages. In normal individuals under normal conditions acetone has been found in the urine and breath in amounts up to 0·02 gramme in twenty-four hours (2). Diacetic acid and β-oxybutyric acid are found only in pathological conditions and are excreted only by the kidneys. In the terminal stages of diabetes mellitus the excretion of the acetone bodies (acetone, diacetic, and β-oxybutyric acids) reckoned as β-oxybutyric acid may exceed 150 grammes in twenty-four hours (3).

At the present time the best evidence is in favour of the view that the source of the acetone bodies is the imperfect oxidation of fat; this may be the fat of the food or the fat of the tissues.

The harmful effects of the excessive production of the acetone bodies are twofold. First: the failure to oxidize these substances means a loss of energy to the body; each gramme of β-oxybutyric acid which is excreted as such, instead of being burned to carbon dioxide and water, means a loss of 4·4 calories (4) to the organism (a loss somewhat greater than for each gramme of glucose which is excreted as such). Second: these organic acids have a direct toxic effect on the tissues, affording the symptoms which are recognized under the general term of 'acid intoxication', and their cumulative effect is believed by many to be the direct cause of coma as seen in diabetes.

In following such cases of disordered metabolism it is well to recognize the considerable loss of energy in order that we may regulate the diet accordingly. For example, a diabetic excreting 50 grammes of glucose and 50 grammes of β-oxybutyric acid in twenty-four hours would show the following loss :—

$$
\begin{array}{lll}
\text{50 grammes glucose} & \times\ 4{\cdot}1 = & 205 \text{ calories} \\
\text{50 grammes } \beta\text{-oxybutric acid} & \times\ 4{\cdot}4 = & \underline{220} \quad \text{,,} \\
\text{Total loss} \qquad . \qquad . & & 425 \text{ calories.}
\end{array}
$$

This represents a loss of about one-sixth of the caloric value of the food ordinarily prescribed for an adult diabetic. For such reasons a knowledge of the quantity of the acetone body output in severe diabetes is quite as important as a knowledge of the amount of sugar excreted. Hence in order that we

may have a clearer insight into the pathological processes in these cases, for purposes of prognosis and therapeutics, quantitative estimations of the excretion of the acetone bodies are indispensable.

There are several methods (5) which have been employed to estimate the degree of acidosis, but while they are desirable, their complexity and expense place them beyond the reach of the average clinician. An extensive experience with those suffering from various degrees of 'acidosis' and numerous studies pursued on this subject have led me to the conclusion that a few simple test-tube reactions will serve to afford information of great value to the clinician in watching the rise and fall of the 'acidosis'. I have proposed the term 'acidosis index', with definite numerical values, in order that for clinical purposes we may have a quantitative expression to denote the degree of acidosis.

If one follows a case in which a condition of 'acidosis' is developing he will first detect in the urine a small amount of acetone; this will gradually increase in quantity, and later diacetic acid will be found (6); when diacetic acid is being excreted in any considerable amount β-oxybutyric acid will also be found. When the 'acidosis' begins to clear up, the β-oxybutyric acid is the first to disappear, followed by diacetic acid and acetone in the order named.

The estimation of the 'acidosis index' depends upon the above facts and upon the delicacy of certain simple tests for acetone and diacetic acid. The following are the tests which I employ for the purpose: 1. *Lange's Test*. In a test-tube containing 5 c.c. of the urine under investigation, dissolve a few small crystals of sodium nitroprussiate, add 1 c.c. of glacial acetic acid; overlay this mixture with 3 c.c. of strong ammonium hydroxide. In the presence of acetone a purple ring will develop at the point of contact between the ammonia and the underlying mixture.

2. *Gerhardt's Test*. This is the time-honoured test for diacetic acid, viz. the development of a Burgundy red colour on the addition of a solution of ferric chloride to a urine containing diacetic acid. For the determination of the 'acidosis index' the following solutions are necessary:—

(a) The 'standard solution', consisting of ethyl aceto-acetate 1 c.c.: alcohol 25 c.c.: and distilled water to 1,000 c.c.

(b) Ferric chloride solution, consisting of 100 grammes of ferric chloride dissolved in 100 c.c. of distilled water.

Take two test-tubes of equal calibre ($\frac{1}{2}$ inch in diameter); put in one 10 c.c. of the 'standard solution' and in the other 10 c.c. of the urine to be tested; add to each 1 c.c. of the ferric chloride solution; allow the tubes to stand a couple of minutes to permit the colour to develop fully, and then compare the colour of the two test-tubes when they are held between the sky and the eye. If the tube containing the 'standard solution' is of a lighter shade than the urine mixture, dilute this with distilled water until the colours match, noting the volume to which it has been necessary to dilute the urine mixture.

By the use of these reactions we obtain a numerical value for the 'acidosis index per litre' in accordance with the following schedule:—

Acidosis Index per Litre.

Lange's test positive }	=	0·5
Gerhardt's test negative }		

Gerhardt's test positive :

Volume of urine solution.

10 c.c.	=	1·0
15 „	=	1·5
20 „	=	2·0
25 „	=	2·5
40 „	=	4·0
100 „	=	10·0

(Intermediate volumes have a proportional index.)

In order to obtain the 'acidosis index' proper, we multiply the value of the 'acidosis index per litre' by the amount of urine in litres passed in twenty-four hours. For example: A patient passed 3,200 c.c. urine in twenty-four hours: when 10 c.c. of this was treated as described above, it was found necessary to dilute this to 75 c.c. in order to match the standard: his 'acidosis index per litre' was therefore 7·5 and his 'acidosis index' was $7·5 \times 3·2 = 24$.

The 'acidosis index' approximately corresponds in value to the total acidosis estimated in terms of β-oxybutyric acid by the more exact chemical methods, i. e. an 'acidosis index' of 10 corresponds approximately to a total acidosis of 10 grammes of β-oxybutyric acid; an 'acidosis index' of 25 equals approximately 25 grammes of β-oxybutyric acid, &c. For the more detailed evidence upon which this clinical quantitative method rests, those interested are referred to my earlier papers on the subject (7) (8).

In utilizing this method it should not be forgotten that substances are frequently found in the urine which give on the addition of ferric chloride a colour reaction not unlike that of diacetic acid; for example, a common error is to assign the development of the wine-red colour after the addition of ferric chloride to the presence of diacetic acid, when it is really due to the ingestion of salicyclic acid or one of its compounds. Urines which give a strong 'diazo' reaction will often give a ferric chloride reaction not unlike diacetic acid. However, if one bears this in mind and in doubtful cases uses a corroborative test for diacetic acid such as Arnold's (9), or other precautions as suggested by Hammarsten (10), he will not be led astray.

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AN EPIDEMIC OF GANGRENOUS DERMATITIS

By F. C. PURSER

With Plate 22

EVEN though it prove a mild affection—as it did, fortunately, in the cases now to be described—gangrenous dermatitis as an epidemic complication of acute disease is sufficiently rare to deserve recording.

On the morning of October 5, 1911, four female patients in one ward of the Hardwicke Hospital, Dublin, presented more or less remarkable examples of this condition. The cases were not under the care of any one physician or one set of nurses. I must thank my colleagues, Drs. O'Carroll, Coleman, and Travers Smith, for permission to report the cases under their care.

All four patients were suffering from enteric fever, and in each case the dermatitis was confined to the buttocks. As the cases differed from each other only in the number and size of the gangrenous patches present it is unnecessary to describe each in detail. By far the most conspicuous case, both in the number and in the size of the lesions, was that of E. F——g, a married woman, aged 47, under the care of Dr. Travers Smith. On each buttock, especially on the outer portion, but also in the natal cleft, were a number of coal-black spots. There were about 250 in all. In size they varied from a tiny pin-head to the cross-section of the kernel of a hazel-nut. The larger ones were somewhat oval, the medium-sized and smaller ones were circular. Here and there irregularly-shaped spots suggested the coalescence of smaller ones. With the exception of a few amongst the smallest, each spot was surrounded by a pinkish-red zone varying roughly in breadth with the size of the gangrenous area. The illustration, made from E. F——g, shows no gangrenous patch without an encircling hyperaemic zone, but in some of the sixteen cases there were such patches, and in the case of E. F——g also there were, though not shown, some very small ones. The larger units were a little elevated and felt lumpy, the outer margins being sharply defined ; the smaller were not appreciably raised above the general surface. The centre of the actual mortification in the larger lesions was below the level of the margins. The surface of all the blackened parts and the entirety of the great majority were quite dry. But from the larger lesions in the case of E. F——g, a greyish-black, diffluent, but not appreciably foetid matter could be squeezed. Her night-gown and the sheets on her bed were stained with this ooze on the day the condition appeared. The necrosed tissue, where not diffluent, was firmly adherent to the surrounding tissues. When as much as possible had been

removed with an instrument a greyish-black ulcer was left. The edges were perpendicular and the depth was about one-fifth of an inch. The illustration gives an accurate idea of the appearances in this case.

M. F., a girl of 19, had nine spots in or near the natal cleft, each one surrounded by a hyperaemic zone. Two spots showed central gangrene about the size of a split pea ; in the remainder the gangrene was less extensive. I excised one patch entirely under local anaesthesia and brought the edges together with a catgut suture. The stitch tore out—the result, I fear, of my inadequate surgical technique—but the wound healed up completely in about sixteen days without suppuration or other mishap. It was dressed with Friar's balsam.

F. C., 27, and E. D., 44, showed five and six spots respectively, all small with narrow reddish zones around.

In every case many spots were in close relation to hair follicles, but I could not be sure that all were. All were moderately severe cases of enteric, but were clear mentally. None complained of pain or discomfort, though their skins were not anaesthetic. On the following day, however, and for some days subsequently, E. F——g and M. F. (with good reason !) complained of considerable soreness in the parts. There was no aggravation of general symptoms in any case, no elevation of temperature or acceleration of the pulse-rate.

On October 6, five males (P. H., M. L., P. L., J. B., J. H.), between 8 and 29 years of age, all suffering from enteric, showed a few spots each, and in the same ward as those affected on October 5 were two fresh cases, M. C. H. (enteric) and E. F——n (croupous pneumonia, delivered of a stillborn six-months child on the second day of her illness, three days before admission from the Union Hospital). J. C., 14 (typhus), had two spots over the 11th and 12th on his right side. In this patient, and in H. R., 19 (enteric), the spots were on the back ; in every other case they were on the buttocks. The ward sister noted the spots on H. R. on October 4, but as I did not see the patient that day my attention was not called to them till October 5. They were very small, and one only of the three had a red areola. M. K., 6 (diphtheria), developed three spots on October 8. She died the following day. This patient was on a different landing from all the others. J. L., male, 19 (croupous pneumonia), developed three spots on October 11.

Whether the necrosis was a post- or a pre-inflammatory condition is impossible to say. The sister and nurses in the wards were absolutely definite as to the absence of any marks on the patients (H. R. excepted) on the night of October 4, and I personally can answer that late on October 5 there was nothing to show that the patients who developed the condition on October 6 were likely to do so. To the best of my belief all the lesions in any one patient appeared at the same time ; at all events there were no second 'crops' or fresh lesions such as one could attribute to inoculation from areas originally involved. Each patch gradually cleared up ; the gangrene shrank, but for days remained firmly adherent unless forcibly removed. The red areola became bluish, then faded and became flat. A ring of suppuration appeared around the gangrene in two spots on M. F. This was the only case in which pus was seen. I thought, without

actually having measured their size, that the spots on E. F——g and M. F. enlarged during the day of October 5. In the other cases any change in size after their first appearance was a decrease.

Every precaution was taken to check the spread of infection. The local treatment was very simple. Some sores were cauterized with liquid carbolic acid, cleansed with methylated spirits, and dusted with boracic acid. In others carbolic acid was not employed. Some cases for which I was responsible were merely dusted over, no other treatment appearing necessary.

Nothing conclusive was revealed by the bacteriological examination of the affected areas. Seven only of these cases were investigated. From spots on E. F——g, M. F., and E. F——n, smears were made on a cover-slip. Each showed a rather short bacillus which was decolorized when stained by Gram's method, and a Gram-staining coccus in very small numbers. From the moist gangrenous matter in another spot on E. F——g, a streak culture on ordinary agar yielded a sparse growth of *Staphylococcus aureus*; a stab-culture in glucose-agar proved sterile. From another spot MacConkey's medium was inoculated; this showed no growth after twenty-four hours, though kept at 37° C. I put the plate away in a drawer, but needing a MacConkey plate after a few days I took this one and found on it a few colonies of moulds and one of a Gram-staining staphylococcus which was not investigated further than to show that it made a lactose and a litmus-milk medium acid. This colony was not unlike a *B. coli* growth. Another colony was the growth of a Gram-negative motile bacillus which gave the reactions of *B. typhosus* in litmus-milk, lactose, glucose, and MacConkey's liquid media. A third sub-culture of this bacillus was not agglutinated by strongly agglutinating serum. Yet another colony, which was thought to be one of *B. typhosus*, would not grow on transplanting.

From M. F—— a stab-culture in glucose-agar from gangrene showed plentiful growth, with formation of gas, of a Gram-negative motile bacillus. This precipitated neutral red, with formation of gas, in MacConkey's medium, clotted milk, and produced acid and gas in lactose and glucose media. After two weeks it had not liquefied gelatine. A bacillus similar to this was isolated from E. F——n. A streak on ordinary agar from a second spot yielded a solitary colony of mould. No cocci grew in media inoculated from these patients.

A gangrenous piece was removed from H. R., and planted surface up on a MacConkey plate. It proved sterile. The red zone around a second patch was cleaned of the superficial epidermis and the serous fluid damping the surface was streaked on agar. This proved sterile, but the spot had been cleansed with iodine before scraping. Similar attempts were made with M. C. H., P. H., and E. D. From the latter two *Staphylococcus albus* grew. E. F——g and H. R. showed a few spots like deep-coloured 'rose spots', which it was thought might be a pre-gangrenous stage of the condition. Smears on agar were made from these, but nothing grew. Except in the case mentioned the skin was cleansed only with soap and water. The spots faded and disappeared in a few days.

The diseased focus removed from M. F. was stained for micro-organisms in

a variety of ways—by Gram's method, methylene blue, thionin blue, and carbol fuchsin.   No organisms were found in the tissues in a large number of sections examined.   Histological examination of these sections showed an ulcer with steep sides extending into the true skin.   Its floor was approximately at the level of the papillae of the hairs.   Both floor and walls were covered with a black or brownish-black structureless material.   The epidermis at the edges of the ulcer was loosened from the corium beneath, its cells were swollen, their outlines lost, and their nuclei stained poorly or not at all.   The connective tissues in the true skin beneath the ulcer had undergone hyaline change or cloudy swelling. The capillaries were congested, but there was little or no extravasation of red blood corpuscles.   Here and there thrombosis was seen in larger vessels.   Mononuclear and polynuclear leucocytes were fairly numerous, most numerous perhaps around the hair follicles.

To sum up, then : In the severer cases, E. F——g and M. F., and in E. F——n, bacilli were found belonging to the typhoid-coli group.   In no other cases were these found.   In these patients the gangrenous patches examined were moist, and as they might readily have become infected subsequent to the parts becoming necrosed one cannot assume that the bacilli were the cause of the necrosis.   Moreover, I am not aware that bacilli of this group cause gangrene when inoculated into the skin.   Other organisms, when found, were staphylococci, aureus and albus, in very small numbers—either of which might have been found in equal numbers in any healthy skin.   Pyogenic organisms certainly may cause gangrene, but there is suppuration as well, and the instances where this occurs are not of such favourable termination as were those under consideration. More especially does this apply to streptococci, which in pure culture or with other organisms (such as *B. diphtheriae*) are found in cancrum oris, noma, and gangrenous tonsillitis and pharyngitis.   But neither are these conditions comparable to that under consideration, and moreover these organisms were not found in any case examined.   On the results of these investigations, then, it is impossible to draw any definite conclusion as to the microbic origin of the lesions.

Failure to find a fundamental explanation of the outbreak, however, must not deter one from advancing a possible one.   The synchronous appearance of the lesions in a number of persons suffering from different diseases, the limitation of the lesions to the buttocks (except in two cases where they were low on the back), and the absence in every patient of signs of renal, pulmonary, or other infarction make it certain that the infection—for infection it surely was—was introduced from without.   It was suggested that the tow used for cleansing the patients was at fault.   There was, certainly, fair reason for entertaining this proposition, for a fresh supply of tow was brought into the hospital on the evening of October 3, and the dermatitis appeared only in those wards where tow from this supply was used.   And after this tow was banned some was used by an oversight in a ward hitherto free, and a case (J. L., referred to) occurred on October 11. On the other hand, at least one-half of the patients cleansed with this tow presented no dermatitis, and repeated bacteriological examination of the tow

showed the presence of no micro-organism other than the non-pathogenic *B. subtilis.*

Though differing in one important respect from the cases already described, a further case of gangrenous dermatitis must be reported with them. On October 26 a boy, A. Fo., aged 3, was admitted as a case of typhoid fever under the care of Dr. Coleman. He was put in the women's ward where the other cases, now nearly cured, were. The child was found to have severe broncho-pneumonia. On October 29 the ward sister called my attention to a spot on the child's buttock. This lesion closely resembled those already described. But above this spot, and just above the crest of the ilium, was a little papule with a round vesicle on its summit. The contents of the vesicle were somewhat turbid. The papule was surrounded by a red area about one quarter of an inch wide. In three days this lesion resembled those in the other cases; the mortified centre was dry and firmly adherent. The earlier appearing lesion had begun as a vesicle in every respect similar to this one. The child died on November 2.

As the unbroken vesicle made secondary infection a lesser probability in this case than in the others one was justified in hoping for more conclusive results from bacteriological examination. The vesicle was opened accordingly with every precaution, and its contents inoculated on various media—blood-serum, agar, glucose-agar. From all *Staphylococcus aureus* and *B. coli* were separated. Anaerobic cultures were made also, both by means of stabs in glucose-agar and by growing on various sloped media in an oxygen-free atmosphere. The same organisms only were found under these conditions. Some of the contents of the vesicle were inoculated (vaccination-wise) into the arm of a healthy man, with the result that there was a zone, about one inch in diameter, of hyperaemia and just noticeable swelling which lasted three or four days. It was attended with considerable itching, but no other inconvenience. The sub-gangrenous matter of the other lesion was examined on corresponding media and the same bacilli were found. After death the lesions were cut in sections; very few bacilli but numerous cocci were seen. The micro-organisms penetrated but a very short way into the living tissues. There was slightly more leucocytic infiltration than in the sections from M. F., but no other noteworthy difference.

At the autopsy it was noticed that there were some two dozen purple-brown, oval or roughly circular spots on the trunk. Their diameter was on an average that of a lead pencil. They were unlike the usual post-mortem discoloration, and were found in equal numbers on the abdomen and the back. Two of these were examined thoroughly for micro-organisms, both in sections and as one would recover typhoid bacilli from a spleen, but none were found. In addition to the broncho-pneumonia, some ten ounces of flaky pus were found in each pleura and about three ounces in the pericardium. Smears of these exudations showed an organism of the classical appearance of *Diplococcus pneumoniae*, but repeated attempts to isolate it failed. It was killed out by motile Gram-negative bacilli. The ubiquitous *B. coli* was isolated from both pleural and pericardial pus. From the latter in addition a bacillus was separated which on agar gave a slightly less

opaque growth than *B. coli*. It grew freely in various media but gave no characteristic reactions in any. In fact it altered no media. From the pleural exudate, besides *B. coli*, a bacillus was separated which fermented glucose and liquefied gelatine. No other medium was altered. Five c.c. of swarming broth-cultures of these bacilli were injected with the interval of a week into the peritoneum of a rabbit—Dr. O'Sullivan kindly did this for me—with no appreciable result in the first instance. The rabbit ate little for three days after injection of the second culture, but otherwise was none the worse.

To make references to the literature on gangrenous dermatitis may seem an undue weighting of my description of this inconsequential little epidemic. But inasmuch as I have found no parallel to it I would refer in a collective way to cases already described, and more especially to those which occurred in epidemics or in connexion with acute disorders. The condition described first by Jonathan Hutchinson as varicella gangrenosa, and subsequently by several observers, will occur to every one's mind. That the Hardwicke epidemic does not come under this heading is evident, for the severity of the lesions was incomparably less grave than in varicella gangrenosa, the lesions were, in practically every instance, confined to the buttocks, and, above all, there were no signs of previous vesicles and pustules. In his original description of varicella gangrenosa, Hutchinson refers to a paper by Whitley Stokes on gangrenous conditions of the skin. This account was published in the *Dublin Medical and Physical Essays* in 1807. It was a description of a disease well known throughout Ireland, but, though very fatal, it had apparently attracted little notice from medical men, for till Stokes gave it the name pemphigus gangrenosus it had been known only by the unscientific but none the less descriptive names of ' eating hives ' and ' the burnt holes '. It appears, too, to have been much more successfully dealt with by women herbalists than by the profession. Stokes, unsuccessfully to my mind, tried to differentiate it from varicella, and Hutchinson is probably correct in assuming the identity of it and varicella gangrenosa. Hutchinson, Crocker, William Stokes, Haward, and others, have recorded cases of multiple gangrenous dermatitis following vaccination.

The Hardwicke epidemic was most widespread in wards devoted to enteric and pneumonia. But while a connexion cannot be denied and is possible, the clinical history of the cases and the negative bacteriological findings give one no reason for associating the condition especially with these diseases. But gangrenous dermatitis of a most severe nature has been described by Stahl complicating typhoid fever. Among a number of American soldiers suffering from enteric and brought from various camps in the Spanish-American War ten showed gangrenous dermatitis. Three of the ten died. Stahl gives reasons for regarding the lesions as embolic in origin, and in two cases that came to autopsy infarcts were found in the lungs, kidneys, and spleen. In these cases bacteriological examination of unbroken vesicles, which preceded the gangrene, showed staphylococci (aureus and albus) and diplococci.

Cases have been recorded complicating erythema nodosum (Demme, quoted

by Hartzell), in which a bacillus was found which, when inoculated into guinea-pigs, caused gangrene. Other cases reported by Mensi and by Eichhoff complicated measles. From Mensi's case *Staphylococcus aureus* and bacilli resembling *Proteus vulgaris* and the diphtheria bacillus were separated. Inoculation of a mixture of the two first named produced gangrene like that they were recovered from. In Eichhoff's case the micro-organism found resembled *Trichophyton tonsurans*.

There is abundant other literature on gangrenous dermatitis that need not be quoted. It all goes to show that multiple gangrenous lesions of the skin, where apparently infective and not obviously tropho-neurotic in nature, are due not to one special micro-organism acting on a body rendered less resistant by any special disease, but may be due to a variety of organisms, some of them well recognized and their usual action well known. These, acting on soils of different suitability and (singly or in various combinations) with different degrees of virulence, may perhaps produce the less usual condition of gangrene. But as these factors are at present unmeasured the explanation, however reasonable, is purely hypothetical.

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EXPLANATION OF PLATE 22.

The plate shows the appearance of the lesions in an early stage in E. F., a female aged 47.

THE ORIGIN OF CHRONIC ULCER OF THE STOMACH IN THE ACUTE VARIETY OF THE DISEASE

By CHARLES BOLTON

With Plates 23–26

FOR a considerable number of years, in fact from the time of Cruveilhier (1), two types of simple ulcer of the stomach have been recognized, the acute and the chronic.

In most text-books acute ulcer of the stomach receives very little attention, and sometimes it is absolutely ignored. Those authors who deal at all adequately with it treat it as being a disease quite distinct from chronic ulcer. In fact it is perhaps the general opinion that the two diseases have entirely different origins. Cruveilhier (2) initiated the idea that chronic ulcer arises from the acute variety, the initial lesion, in his opinion, being an inflammation of the gastric follicles occurring as a part of a generalized gastritis.

The term ' follicle' was formerly applied to the gastric glands, and was used in this sense by Abercrombie (3). Brinton (4) discusses the question and thinks ' it would be a great advantage if the terms " tube " and "follicle " were attached to distinct structures, the latter (as its etymology suggests) being restricted to the closed sac formed by the lenticular or solitary gland'. Carswell (5), in his book on Pathological Anatomy, uses the term 'follicle' to signify a lymphoid structure and gives an illustration of ulceration commencing in this situation. A perusal of his description of follicular ulceration leaves no doubt in the mind as to what Cruveilhier meant by the expression ' ulceration commencing in the lymphoid follicles of the stomach'. He likens these structures to the solitary follicles of the intestine and shows illustrations of enlargement of these lymphoid follicles in the stomach in cholera, which clearly demonstrate what he wished to imply by the term 'follicle'. He also describes typhoid fever as 'acute follicular enteritis'. Ulceration commencing in the lymphoid follicles of the stomach has therefore been recognized for almost a hundred years. Rokitansky (6) also supported the view of the acute origin of chronic ulcer, but he thought that the ulcer commenced as a ' haemorrhagic erosion ' or a ' circumscribed sloughing of the mucous membrane ', and that it was 'in no way connected with gastritis '.

From time to time many observations have been recorded which appear to me to support the idea of the acute origin of chronic ulcer in greater or lesser degree.

The evidence obtained from these observations falls into several groups.

1. In chronic infective diseases, in which it is not uncommon for acute ulcers of the stomach to occur, there may sometimes be found ulcers with thickened edges and bases.

It might be questioned whether these thickened ulcers were actually due to the infections, but this supposition is rendered more certain in those cases in which both acute and thickened ulcers are found together in the same stomach.

In Cock's case (7) of diffuse inflammation of the leg, of several weeks' duration, there was found a superficial acute ulcer in both the duodenum and colon and an ulcer the size of a shilling on the small curvature of the stomach. It had chronic characters, the edges were smooth and raised and the base formed by the peritoneum.

Colombo (8) described three cases. In one case of gangrene of the leg and arm there were two ulcers present in the pyloric region of the stomach. Their bases were formed by the muscular coat of the organ and the peritoneum was thickened and adherent to the pancreas. In a second case of chronic dysentery there was a funnel-shaped ulcer of the posterior wall of the stomach with raised edges. In a third case of cancer of the uterus an ulcer of the stomach presenting chronic characters was found.

Dittrich (9) recorded two cases, one of chronic dysentery and the other of cancer of the uterus, in each of which there was an ulcer of the stomach having chronic characters.

Papellier (10) mentions two cases of chronic tuberculosis, in one of which were found some superficial lesions of the mucous membrane together with an ulcer on the posterior wall of the stomach near the small curvature. The ulcer was a quarter of an inch in diameter and had a fibroid base formed by thickened peritoneum. Four cicatrices were grouped around the ulcer. In the second case three ulcers were found in the pyloric region on the greater curvature. Two of the ulcers would just admit a pea and had recent black sloughs attached to their bases, whilst the third was older, had indurated edges, and penetrated to the peritoneum.

Chambers (11) also quotes a case of chronic phthisis in which three ulcers with raised and thickened edges were found on the middle of the smaller curvature of the stomach.

There cannot be any doubt that such cases are common enough, and that the ulcers showing these characters of chronicity were originally acute, and the result of the infective disease associated with them. Of course it is possible that a patient, the subject of chronic gastric ulcer, might acquire an infective disease, which would give rise to additional acute ulcers, but such a case should be readily recognized. For instance, the peritonitis resulting from the perforation of a chronic ulcer may give rise to acute ulcers in the mucous membrane.

There is a specimen in the museum at University College Hospital (*Medical Catalogue*, No. 3051 C) illustrating this point. The patient was operated upon for perforation of a chronic ulcer. He went on well for a few days and then died from a second perforation.

At the autopsy a large thickened chronic ulcer and several smaller ones, also old and thickened, were found on the smaller curvature of the stomach, one of which had given rise to the original perforation. A second series of ulcers was found lying near the greater curvature. They were all of the same age and acute, they were cleanly punched out, had blackened bases, and one had perforated. There is not the smallest doubt that this second series of acute ulcers resulted from the infection of the peritoneum caused by the first perforation.

The mere association, therefore, of acute with chronic ulcer in the same stomach by no means proves the acute origin of the chronic ulcer present. Still, it is not uncommon to find such an association in patients who are suffering from simple chronic ulcer and in whom no other cause than gastritis can be found to account for the acute ulcers as demonstrated by Nauwerck (12), Miller (13), and others. In such cases it appears to me that the origin of the chronic is identical with that of the acute ulcers.

Gerhardt (14) described three cases of gastritis in which he showed the connexion between 'erosions' and ulcers. On the other hand, Langerhans (15) quotes a case in which there were many small 'haemorrhagic erosions' and three large ulcers, with transitional forms between. He regards this as being a very exceptional case, as he thinks that chronic ulcers result from a primary affection of the blood-vessels in most cases, whilst catarrhal inflammation of the mucous membrane and crampy contractions of the stomach give rise to 'erosions' and very seldom to chronic ulcer.

It was Virchow (16) who originated the idea that spasm of the muscular coats of the stomach or portal stasis might cause haemorrhagic infiltrations into the mucous membrane and resulting ulcers. Key (17) continued this idea of venous stasis due to spasmodic contractions of the gastric walls, and Rindfleisch (18) considered that 'the act of vomiting, by temporarily arresting the return of blood, causes minute extravasations from the superficial venous radicles of the gastric mucous membrane', and that simple ulcer of the stomach originated in such haemorrhages. He quotes a case in support of this hypothesis in which several small haemorrhages, a larger circular haemorrhage, and a perfect simple ulcer of the same size were found after death. The case was one of strangulated hernia, so that the probable cause of the haemorrhages was not the act of vomiting but bacterial infection.

Bazy (19) also saw a case which showed all intermediate stages between superficial ulceration of the mucous membrane and typical ulcer. I am not concerned here with the particular kind of initial lesion that most frequently develops into chronic ulcer, because the material at hand is insufficient for this purpose, and such patients usually die with fully developed ulcers. I quote these few cases in support of the view that, whatever its origin may be, acute ulcer of the stomach is able to acquire chronic characters.

2. When a patient suffering from chronic ulcer of the stomach acquires an infective disease which is known to give rise to acute ulcer, it is not uncommon for the chronic ulcer to commence spreading acutely. In the recorded cases death

has occurred owing to a sudden attack of haematemesis, to perforative peritonitis, or to invasion of an organ, a thickened chronic ulcer being found at the autopsy. Thus Reimer (20) observed such a case during an attack of measles ; Starcke (21) during pneumonia ; Merkel (22) in empyema and pericarditis ; Von Gunz (23) in scarlet fever ; Lebert (24) in pneumonia and double pleurisy ; Guttmann (25) in pleurisy, the old ulcer which was adherent to the diaphragm perforating into the pericardium ; Finney (26) in rheumatism and pericarditis, the ulcer perforating into the left ventricle of the heart, which was adherent to the diaphragm ; Cade (27) during an eruption of boils ; Debove (28) in inflammation of the axillary glands ; Fitz (29) in follicular tonsillitis ; Battams (30) in salpingitis ; and many others. There is, therefore, evidence that an infection of the body, sometimes very slight apparently, may cause an originally existing ulcer to spread acutely. I have seen two cases of this nature lately at University College Hospital and they have been already published (31). They were both cases of perforative peritonitis due to chronic ulcer, one gastric, the other duodenal. Both had pyloric stenosis, and both commenced bleeding a few days after the operation for perforation.

The autopsies showed that in the former case an acute extension of the original ulcer had occurred in the mucous membrane, producing a triangular area extending from the ulcer, and denuded of its mucous membrane ; and that in the latter case an acute ulceration had commenced in the edge of a gastric ulcer involving the cardiac orifice, and had extended up the whole circumference of the oesophagus for a distance of about four inches. I have already said that these cases had pyloric obstruction. That pyloric obstruction alone, in the absence of a general infection of the body, is sometimes able to cause an already existing ulcer to extend acutely I have shown experimentally (32), and there is no doubt that it played a part in the above cases as the pyloric stenosis was unavoidably produced at the operations.

3. An ulcer of the stomach may first declare its presence by symptoms some weeks or months after an infection which is known to be able to give rise to acute ulcer. Such ulcers have been found at operation or after death, and have had clinical histories and post-mortem appearances absolutely like those of simple ulcer of the stomach as seen in medical practice in which no definite sign or history of infection can be obtained.

Such cases have been described as occurring after infective diseases by Cazeneuve (33), Codivilla (34), Mikulicz (35), Régnier (36), Morot (37): after metritis and peritonitis by Bucquoy (38): after dysentery by Bourcy (39). Cases of haematemesis occurring several weeks or months after a local or general infection have also been recorded by Letulle (40), Fabriès (41), and many other observers. A case of this description [1] occurred at University College Hospital in 1910, seven months after operation for perforation of the appendix in which general peritonitis was present and which was followed by the formation of local abscesses.

[1] *Hospital Register*, No. 527. Dr. Risien Russell.

Ulcers have been found in the stomach or duodenum several weeks after the occurrence of burns, by Cooper (42), Wilks (43), Keate (44), Mayo Robson (45), and others. The specimen from the case described by Cooper is at present in the museum at University College Hospital Medical School (*Surgical Catalogue*, No. 1582). It consists of a thickened ulcer adherent to the pancreas, which is exposed in its base.

It must be admitted that the above observations lend some support to the view of the acute origin of chronic ulcer of the stomach.

Many ideas have been formed with regard to the nature of the initial lesion which gives rise to chronic gastric ulcer, and much experimental work has been undertaken with the object of producing ulcer of the stomach. In all cases the supposed or experimentally produced initial lesion has really involved an acute process. In the human subject such lesions are the actual causes of acute ulcer, and they result in the production of acute ulcer in animals.

The pathology of chronic ulcer of the stomach is closely bound up with several different processes, and in studying this subject it is essential to distinguish between these processes, and to study them separately, a mode of procedure which has not hitherto been adopted.

Thus the acute process by which the initial loss of substance is formed is essentially different from the chronic process which leads to thickening of the acute ulcer and transforms it into a chronic ulcer. The process by which both the acute and chronic ulcers spread occurs with varying degrees of acuteness, and the precise factors taking part in this process may be the same as, or different from, those involved in the process of production of the initial lesion. Again, the factors causing an arrest or a delay in the healing of the ulcer require a separate consideration. This communication is especially concerned with the *mode of spread and the early thickening of acute ulcer*, and an attempt will be made to show in what manner this lesion is transformed into a chronic ulcer. In the cases described I am unable to say what was the initial lesion, and that part of the subject is beyond the scope of this paper. It will, however, be of advantage if a definite idea of what is implied by the term 'acute ulcer' is first given, because the term 'erosion' has crept into common use and is applied in different senses by different writers.

DEFINITION.

Cruveilhier (46) in 1821 was the first observer to describe 'erosions or haemorrhagic ulcerations', by which term he meant losses of substance resulting from localized haemorrhage into the mucous membrane, and considered that they commenced in the capillary network. He also calls superficial ulcers beginning in other ways 'erosions'. Rokitansky (47), writing at a later date, likewise uses the term in its wider sense, and thinks that 'haemorrhagic erosions' occasionally arise in the glands of the mucous membrane.

At the present time some authorities apply the term 'erosion' indiscriminately

to any acute loss of substance, whether it penetrates deeper than the mucous membrane or not, whilst others limit it to lesions involving the superficial portion of the mucous membrane.

Others, again, distinguish it definitely from ulcer and confer upon it the dignity of a special disease. Irrespective of the origin of the disease the term 'haemorrhagic erosion' is frequently applied to follicular ulcers and ulcers of necrotic origin; thus the 'exulceratio simplex' of Dieulafoy, which is probably a follicular ulcer, is often called 'haemorrhagic erosion', and the same lesion when it reaches the peritoneum is called 'acute perforating ulcer'.

For the further advance of knowledge in the pathology of gastric ulcer it is essential, therefore, that a more precise nomenclature should be adopted.

I have pointed out elsewhere (48) that *from the point of view of morbid anatomy* an 'erosion' must be regarded as a superficial ulcer, and that when once formed there can hardly be a clear distinction between them. Each of the initial lesions mentioned below may give rise to a superficial or deep ulcer, so that if we wish to distinguish definitely between an 'ulcer' and an 'erosion' the latter term should not be applied to a superficial ulcer. *From the point of view of general pathology* or the process of formation we can, however, distinguish between an erosion and an ulcer. In infective disease, purpuric conditions, and severe anaemias, profuse haemorrhage may occur from the mucous membrane of the stomach in the absence of any ulcer whatever. In such cases it is not uncommon to find at the autopsy superficial erosions having the appearance as if the superficial layers of the mucous membrane had been lightly rubbed off with the finger. These erosions are *mechanically* produced by the escape of blood from the surface and are comparable to abrasions and injuries of the surface which heal rapidly, have no tendency to spread, and cannot be called ulcers; they are in fact 'haemorrhagic erosions'. In the conditions of gastritis and passive congestion of the stomach bleeding may occur from the mucous membrane, the blood escaping from the enlarged capillaries and breaking through the surface of the mucous membrane, thereby producing 'erosions'. It is more useful, in my opinion, to reserve the term 'erosion' entirely for this condition and definitely to distinguish it from 'ulcer', which is *produced by the gastric juice acting upon a damaged portion of the mucous membrane*, and which may involve the mucous membrane only or penetrate to the peritoneum.

FORMATION OF ACUTE ULCER.

Our knowledge of the processes leading to the formation of the initial loss of substance in the mucous membrane is very deficient, because opportunities for the post-mortem examination of specimens are not frequent.

We *do* know, however, that in the human subject such losses of substance arise chiefly in three ways: (1) by necrosis of a localized portion of the mucous membrane; (2) by a localized interstitial haemorrhage into the mucous

membrane ; (3) by inflammation and softening of a lymphoid follicle of the mucous membrane.

All these processes are acute, and result in the death of the tissue affected, or so damage it that it falls an easy prey to the action of the gastric juice. In either case the gastric juice acts equally rapidly and the tissue is speedily removed. In my own experiments (49), when the gastric cells were exposed to the action of gastrotoxin the gastric juice produced necrosis in a few hours and the whole tissue was removed within twenty-four or forty-eight hours. The same feature is observed in the human subject in the case of acute gastric ulcer resulting from burns and infective disease. When once the dead tissue is removed an acute ulcer results, and, unless the ulcer is incompletely formed, or other lesions which have not yet developed into ulcers exist, it is quite impossible to say from an examination of the specimen in what manner the ulcer took its origin. It is quite true that haemorrhages into the mucous membrane may assume the form of long black streaks or irregular blotches, and that the ulcers resulting from them may be of a similar irregular shape ; and also that follicular ulcers are often tiny and scattered throughout the surface of the stomach. But typical round ulcers, few in number or single, may and commonly do result from an interstitial haemorrhage or an inflamed follicle. It is probable that acute ulcer may have other origins of which we are at present ignorant, so that judged from the standpoint of general pathology there are several varieties of acute ulcer, whilst from that of morbid anatomy we are unable in most cases to recognize these varieties. It is probable that any variety of acute ulcer is capable under suitable conditions of undergoing the changes to be described later and developing into chronic ulcer, but in the present state of our knowledge it is not permissible to say which kind of ulcer most commonly undergoes such changes or whether there is any variety of ulcer which invariably does not.

The Fate of the Acute Ulcer.

1. *Normal Healing.*

In the majority of cases an acute ulcer commences to heal at once, and the process of cicatrization is completed in so far as the scar is covered with rudimentary mucous membrane in three or four weeks according to the size of the ulcer.

This is proved by experiments upon animals, in which acute ulcers, however produced, conform to the above rule. It is also proved in the human being by the healing of injuries inflicted upon the stomach, by the number of scars found after death, and by direct observation. The number of scars found after death is known to be considerable, but the statistics compiled by various observers deal chiefly with chronic ulcer, and it is in connexion with the acute variety that I am now speaking. The scars of acute ulcers are very often missed unless some special method of observation is practised (50). Clinically, acute ulcer of the stomach occurs in three chief types of cases: (1) acute infections and intoxica-

tions, (2) chronic infections, (3) simple acute ulcer as commonly met with in medical practice, which is found either in association with some other disease, with which it may or may not have any connexion, or in the absence of any other obvious disease or infection of the body. Even in regard to this third class evidence is accumulating which shows that, at all events in some of the cases, an unsuspected focus of infection, as for instance chronic appendicitis, may be the cause of the ulcer.

Of 100 cases of acute ulcer occurring in various infective processes, the literature of which I have examined, in 39 one ulcer only was present, and in 61 the ulcers were multiple.

In the acute infective cases all the ulcers are in an open condition and scars of acute ulcers are only rarely seen (51), whilst in the chronic infective cases it is not uncommon to find partially healed ulcers and scars together with recent ulcers in the same stomach (52). In the third class I have found that scars together with open ulcers are found in more than half the cases. The patients belonging to this class do not often die, and the available material is small, so that I have only been able personally to examine thirteen cases. Of these thirteen cases, counting both scars and ulcers, in five there was a single lesion, and in eight multiple lesions were present, giving percentages of $38\frac{1}{2}$ and $61\frac{1}{2}$ respectively. These numbers agree closely with the percentages given above for the infective cases, but in this case the multiplicity is chiefly due to the number of scars present. Thus, in six of the thirteen cases there were ulcers only, in five of which the ulcer was single and in one of which multiple ulcers were present. In the remaining seven cases there were ulcers and scars, in five of which the ulcer was single and in two multiple ulcers were present, the scars being single in three instances and multiple scars being present in four. So that a single ulcer was present in ten out of thirteen cases, or in about 77 per cent. On the other hand, in the seven cases with scars, the latter were multiple in four instances, or in about 57 per cent. A single ulcer is also more likely to be found than multiple ulcers, whether scars are present or not.

In no case were there more than six lesions present in the same stomach, whilst in the infective cases several hundreds may occasionally be present, although even in these cases there are usually no more than from two to eight.

These numbers are very small and only provisional conclusions can, therefore, be drawn from them, but it appears that the longer the patient is likely to live, the more likely are scars to be found in the stomach after death, whether the ulcers are of infective origin or not.

Not only does acute gastric ulcer very commonly heal, but it tends to recur in the same individual, because it is unlikely that the multiple scars found in more than half the cases were all the result of ulcers produced at the same time, since a single open ulcer is found in 77 per cent. of cases.

Direct observation also confirms the view that acute ulcer readily heals. During the formation of an acute ulcer it is not uncommon for an artery in the submucous coat of the stomach to be opened up. In such cases it sometimes

happens that the patient dies, although such an event only very rarely occurs at once.

It is the repeated haemorrhage which kills the patient, so that death is usually delayed for a longer or shorter time. At the autopsy in such cases, as I pointed out in a previous paper (53), the edges of the ulcer usually show distinct signs of healing. In fact the base of the ulcer may be almost entirely covered with epithelium up to the open mouth of the artery, which then appears as a hollow projection in the centre of a scar, from which blood can be squeezed.

In spite of the condition of anaemia of the patient the ulcer has rapidly healed. Such a lesion is very difficult to find even after the stomach is removed from the body and washed.

It may, therefore, be taken as proved that acute ulcer of the stomach in man usually heals rapidly, and confirmation of this statement is afforded by the fact that acute ulcer in animals, however produced, likewise heals rapidly.

2. *Delayed Healing.*

Experiments upon animals, in which an acute lesion of the gastric mucous membrane has been produced and in which subsequent procedures have been adopted to prevent the healing of the lesion, have not resulted in the production of a chronic ulcer but have merely caused a delay in the healing. My own experiments (54) in this connexion have shown that retention of food in the stomach, either due to the character of the food itself or to a condition of muscular insufficiency of the stomach, is an important cause of the delay in the healing of an acute ulcer. In such a case the base of the ulcer is liable to become necrotic from the prolonged action of the gastric juice, or to be excessively fibrous, so that the epithelium grows over the base with greater difficulty and the newly-formed mucous membrane is not so perfectly regenerated. It is, therefore, to be expected that a similar condition prevails in the human subject, and in 1910 (55) I published a very typical instance of this. Such cases cannot be rare, but are only to be recognized by careful examination. The patients are not very likely to die, because they have got over the initial stage of acute ulcer, which is the most precarious time. This type of ulcer can be recognized by the following points, and in these points it absolutely corresponds with similar ulcers in animals. The ulcer is of small size and corresponds in dimensions with the original extent of the lesion, which can easily be gauged, because the muscularis mucosae is not re-formed during healing and regenerated mucous membrane can be distinguished microscopically from normal mucous membrane. There is more thickening of the base, whether the muscular coat had been originally perforated or not, than occurs in the condition of normal healing, and more scarring of the wall of the stomach results. If regeneration of the mucous membrane has barely commenced, the edge of the ulcer ends abruptly and is smooth and rounded, so that the ulcer appears to be punched out. The edge will, however, be found to

slope if the epithelium has commenced to grow over the base.   The base is smooth and has grown up more or less level with the mucous membrane.   The ulcer may be contracted to an oblong or oval form and the surrounding mucous membrane more or less thrown into radiating folds and lines, owing to shrinkage of the fibrous tissue in the base.

The clinical history of such a case may indicate the age of the ulcer, but only reliably if an attack of haemorrhage has coincided with the formation of the acute ulcer, so that the period at which the latter appeared can be decided.

What proportion of chronic ulcers results from the mere arrest of healing of an acute ulcer it is impossible to say.   Not many, I think, because in the vast majority of chronic ulcers which I have examined there is evidence that the ulcer has been spreading.

It is quite true that now and then one meets with small chronic ulcers with thickened bases in which digestion is apparently going on, although there is no progressive lateral extension ; but most of these ulcers have been extending for a certain time, the process of extension has been arrested, and the small size of the ulcer is due to contraction of the fibrous base.

3. *Extension of Acute Ulcer.*

In an acute ulcer which is extending two processes are to be recognized : a destructive process by which the ulcer increases in size, and a secondary inflammatory process by which it becomes thickened and acquires the property of chronicity.

An acute ulcer spreads in two directions, *laterally* by extension in the mucous membrane and also *in its depth*.   The resulting shape depends upon the relative amount and rapidity of extension in each direction, and upon the degree of inflammatory thickening which has taken place.   It may be spreading laterally in *each* direction, but sooner or later its extension in one or more directions comes to an end, so that whilst one edge remains stationary another may be extending.   The lateral extension entirely depends upon destruction of the mucous membrane.

Extension in the depth of the ulcer depends upon digestion of the walls of the stomach forming the base of the ulcer, and of the inflammatory tissue which has been secondarily formed.   If the lateral extension occurs equally in each direction, the ulcer will be round ; if in one direction more rapidly than in the other, it will be oblong or more irregular in shape.   The same result is brought about by the arrest of extension of some particular edge.   Two ulcers may meet and join together during their lateral extension, also giving rise to an irregular shape, the line of junction being marked for some time by an elevation in the floor of the resulting ulcer.

In an actively extending acute ulcer the mucous membrane is destroyed first and the edge of this appears to be sharply punched out.

Internal to this edge of mucous membrane is to be seen a thin ring of submucous tissue about to be destroyed, whilst the base of the ulcer is formed of muscular tissue, which is most excavated in the centre, as this portion has been exposed longest to the action of the gastric juice. At a further stage the excavated portion of muscle in the centre becomes perforated and the sub-peritoneal tissue exposed. Unless this latter structure has already become thickened the peritoneum may necrose and perforation occur or adhesions form. Inflammatory thickening and adhesions of the omentum are commonly present although the ulcer has not perforated. Two or three weeks are quite a sufficient time for such adhesions to form. The sides of an acute extending ulcer are, therefore, terraced and the cavity funnel-shaped and deepest in the centre. The more rapidly it has extended laterally the more sloping will be the edges of the cone and the more shallow will it appear, the base being in such cases not thickened to the naked eye (Figs. 1, 7). If it has extended slowly there is more time for inflammatory thickening to have taken place and the result will be a deep cone-shaped cavity.

One edge, which has extended more rapidly in the superficial direction than the other, will be more sloping, and the apex of the cone then becomes eccentric. Such an ulcer may stop extending laterally, but show no tendency to heal. Digestion, however, of the base of the ulcer still goes on more or less slowly and small sloughs separate from the sides, so that the mucous membrane at the edge becomes overhanging and undermined and the cavity more globular in shape (Fig. 6). The base of such an ulcer is formed of thickened peritoneum or inflamed omentum, or it has become adherent to an organ or tissue which offers consider-able resistance to the action of the gastric juice. If not, perforation sooner or later occurs, but thickened peritoneum seems to offer a considerable resistance to digestion. The perforation occurs by a portion of the peritoneum becoming necrotic and giving way, the ragged aperture soon being converted into a smooth round hole. Such ulcers are usually described as chronic, and they are certainly on the way to becoming chronic, but these cases of which I speak have a short history, and my experiments on animals have demonstrated that quite a consider-able amount of thickening may occur in a few weeks. The other class of case in which extension has occurred rapidly in a lateral direction is perhaps more interesting still. In these cases the ulcer is quite shallow and the thickening is inappreciable, except at the part which has been longest formed.

If the ulcer be extending equally in all directions the mucous membrane is sharply punched out all round and surrounds a narrow ring of submucous tissue (Fig. 1). The base is formed of muscular tissue alone or with subperitoneal tissue and fat showing through in the centre. Such an ulcer may be as large or larger than a shilling. A more interesting condition, and one which closely simulates a chronic ulcer, is that in which one edge of such an ulcer has stopped extending laterally. This edge becomes overhanging by separation of sloughs of the under-lying stomach wall and is more or less thickened and raised (Fig. 4). The other edges are terraced with the mucous membrane sharply punched out, the sides

sloping more or less obliquely in proportion to the acuteness of the process of lateral extension. Sometimes at one spot the mucous membrane is extensively destroyed, laying bare a large tract of submucous tissue, whilst internal to this the muscular coat is also extensively visible, the side sloping very gradually indeed towards the base. At such a spot extension is much more rapid than at another where the edge slopes more abruptly. This must be carefully distinguished from the condition of commencing cicatrization.

A healing edge is not terraced. The base at this spot is smooth and slopes away towards the centre, and the mucous membrane becomes thin and gradually lost on the surface of the granulation tissue (Fig. 8). The base of such an extensive ulcer is formed of peritoneum slightly if at all thickened, although the omentum externally is inflamed and matted. Large vessels commonly ramify in the base and very often one or more are opened and present bleeding-points. Perforation may have occurred at one spot.

The blood-vessels offer a considerable resistance to digestion. They are sometimes cleanly dissected out and occasionally may be seen running for some distance along the edge of the ulcer.

Broadly speaking, this shallow type of ulcer appears to be commonly situated on the small curvature of the stomach or near it, whilst the funnel-shaped ulcer, which is smaller and tends to perforate, is more commonly situated on the anterior or posterior wall, where the blood-vessels are not so large. The fact that a *chronic* ulcer on the small curvature is most likely to bleed, whilst a similar ulcer on one of the surfaces is most likely to perforate, is a fact well known. I particularly wish to emphasize the similarity in the case of acute spreading ulcer. I do not intend entering into any discussion with regard to the factors influencing the rapidity and mode of spread of the ulcer, or the occurrence of the secondary inflammatory process, because the facts at hand concerning these processes are at present too ill defined, and in this paper I merely wish to demonstrate the fact that acute ulcer extends, thickens, and becomes chronic, and also the morbid anatomy of the conditions produced.

The microscopical examination of these cases is very interesting because it shows the transition from acute to chronic ulcer in a striking fashion. In all cases the mucous membrane at the edge of the ulcer and for some distance around shows the changes characteristic of gastritis. The whole mucous membrane of the stomach may show such a condition, but in other cases the inflammation is limited to a small region surrounding the ulcer.

I have already mentioned that gastritis with inflammation of the lymphatic follicles is one cause of acute ulcer of the stomach, and it is not surprising, therefore, that an acute spreading ulcer should be found in a stomach the subject of a generalized gastritis. But in those cases in which the inflammation is limited to the region of the ulcer there is no reason to believe that this inflammation is of a different nature from that which affects the other coats of the stomach—namely, that it is a secondary condition to the presence of the ulcer. I shall not attempt fully to interpret all the changes in the mucous membrane in

this communication, because they are of a very complicated nature, and the material I have had to work with is not enough from which to draw many general conclusions. I will merely mention that in one case the more rapidly spreading edge, with widespread destruction of the mucous membrane, was affected with a more intense form of gastritis than that affecting the more slowly spreading edge. Whether this indicates any definite relation between the condition of the mucous membrane with regard to inflammation and its digestion by the gastric juice must be left for future observations to decide, especially in view of the fact that the presence of gastritis is no impediment to healing. The cells of the inflamed mucous membrane proliferate readily, and, in those cases which are healing, cover the granulation tissue of the base rapidly, growing down into the cellular stroma in the form of glands. So that one may see at the edge of the ulcer original glands embedded in the cellular stroma and dilated into cysts, newly-formed glands between them, and newly-formed epithelium covering the surface. The appearances presented by the proliferation of this inflamed mucous membrane are extremely difficult to interpret, and it sometimes seems as if the newly-formed mucous membrane itself became inflamed and that many of the glandular mucous cysts were of new formation. It is difficult to draw a hard and fast line between the newly-formed stroma in which the young glands are proliferating and the inflammatory stroma occurring between the original glands as the result of irritation.

At the *spreading edge* of an acute ulcer the submucous tissue is seen to be slightly thickened and the muscularis mucosae by this means elevated from the underlying muscular coat for a short distance. It is finely fibrous, and infiltrated more or less with round cells, especially under the muscularis mucosae. The coats of the vessels embedded in it may be thickened. On the one hand it rapidly passes into the normal submucous tissue at a short distance from the edge, and on the other into the base of the ulcer, where it has the same characters as at the edge, is thickened, fuses with the muscularis mucosae, and forms the peripheral part of the floor of the ulcer. Patches of necrosis can be seen in the superficial layers at its inner edge, by the separations of which it disappears, laying bare the muscular coat or subperitoneal tissue in the centre of the base of the ulcer (Fig. 2). The bundles of muscular tissue have between them an infiltration of cells, and the peritoneum may be microscopically thickened also. The muscularis mucosae at the edge of the ulcer is thicker and more indistinct than normal, and gradually blends with the submucous tissue at the edge of the ulcer.

The thickening of the submucous tissue is an important condition, because it constitutes the first stage in the thickening of the edge of the ulcer, which gives it the character of chronicity. The submucous thickening is more marked than that in the other layers, and this fact also applies to chronic ulcer, in which it has been recognized for some years (Fig. 11). In cases in which the mucous membrane is being rapidly destroyed the submucous tissue is not thickened immediately under the mucous membrane, but only in the base of the ulcer, the

inflammatory thickening in its formation not being able to keep pace altogether with the destruction of the overlying mucous membrane.

The mucous membrane of the edge, as I have already mentioned, shows varying degrees of gastritis. There is a considerable degree of round-celled infiltration, and towards the edge of the ulcer the glands become shorter and fall over towards the base, sometimes lying almost parallel with its surface. The cells in the tubes tend to desquamate, and at the extreme edge the mucous membrane is composed merely of strands of interstitial tissue, with rows of desquamated gland cells between them; it is necrotic on the surface and infiltrated with round cells. The lymphoid follicles in the immediate vicinity are enlarged, spread out, and become insensibly continuous with the round-celled infiltration. Sometimes the glands have mostly disappeared for a little distance beyond the edge, the surface of the mucous membrane being very uneven and necrotic and the tissue chiefly consisting of round cells, strands of interstitial tissue, and a few groups of gland cells in places, the whole thickness being much less than that of the normal mucous membrane.

The examination of an *edge which has stopped extending* shows that the submucous tissue is very considerably thickened, and that this thickening extends for some distance from the edge, where it gradually thins and fades imperceptibly into the normal submucous tissue. It has, therefore, the appearance of a wedge, the base of which forms the side of the ulcer and raises up the mucous membrane separating it from the muscular coat (Figs. 3, 4, and 6). It consists of a fibro-cellular material which is fairly vascular, the vessels of which are a little thickened. The free end of this thickened submucous tissue is necrotic and gradually disappears, undermining the mucous membrane, whose free edge, therefore, may bend slightly down towards the base of the ulcer and appear somewhat retracted.

There is no doubt that when the muscular coat is perforated in acute ulcer, its retraction turns in the edge of the mucous membrane; but this bending down of which I am speaking is not due to muscular retraction, it is due to undermining of the mucous membrane by digestion of the thickened submucous tissue. Sometimes the deeper portion of the submucous tissue has completely disappeared, with the result that the mucous membrane at the edge has collapsed on to the muscular coat, a narrow cleft extending in between the two.

At some distance from the edge of the ulcer there is commencing infiltration of the muscular coat with cells, and the muscle fibres are degenerating. This condition increases towards the edge and the infiltration becomes continuous with, and of the same nature as, the submucous tissue.

Bundles of muscle fibres can still be recognized at the edge of the ulcer, embedded in the fibro-cellular tissue which extends through them from submucous to subperitoneal tissue, which, together with the peritoneum, is also thickened. The free ends of the muscle fibres become necrotic in the same manner as the submucous tissue and separate as sloughs. In this way the previously terraced edge of the ulcer becomes thicker and undermined, the change being brought about

by a secondary inflammation, which spreads outwards into the wall of the stomach, and by digestion of the exposed parts of the sides and base of the ulcer. The base of the ulcer eventually becomes formed of subperitoneal tissue infiltrated with cells and thickened, the superficial strata being necrotic in a thin layer. In places masses of fat can be seen projecting into the floor of the ulcer. The walls of the vessels embedded in the fibrous tissue are thickened secondarily.

The mucous membrane at such a point is of normal depth almost to the extreme edge. The glands are well formed, often dilated and transformed into mucous cysts, the cells being flattened out, and infiltrated with round cells to varying extents. At the extreme edge the glands become rapidly short and bend over towards the base of the ulcer. There is here considerable interstitial fibrosis and the mucous membrane commonly ends by fusing firmly with the superficial layer of the submucous tissue, forming a smooth edge. The muscularis mucosae broadens out towards the edge, becomes cut up by round cells, and the muscle cells degenerate and blend with the submucous tissue. The whole edge of the ulcer may have this appearance, or only one side, whilst extension is going on in the other directions with varying degrees of acuteness. All these steps may be found in the same ulcer, and ulcers in this condition may be present in the same stomach with more recent ones in which the process is just commencing.

In those cases in which the whole ulcer is healing, the changes are very similar to those which occur in the healing of acute ulcer in animals, the only difference lying in the fact that the mucous membrane is inflamed in the former.

I was able to show experimentally (56) that the chief obstacle to healing lies in the condition of the base of the ulcer, not in the overgrowing epithelium, and so it is in these cases, for when once extension of the ulcer has stopped, although gastritis is present, the epithelium readily proliferates and, if the necrotic portions of the base have separated and the latter has become covered with granulation tissue, grows over the base in a single layer to develop later into glands as is usual in healing. The granulation tissue does not always grow up level with the mucous membrane, but the latter accommodates itself to the resulting depression as in animals. The amount of contraction of the stomach wall depends upon the extent of the ulcer both laterally and in the depth. When the peritoneum has been exposed the cicatrix extends throughout the thickness of the wall of the stomach.

4. *Clinical History.*

The following table gives the analysis of the clinical symptoms of the cases described in this paper:

Case 1. F.; aged 53. **Indigestion** absent. **Pain** absent. **Vomiting** uraemic. **Rigidity** absent. **Tenderness** absent. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Cardiac half of small curvature and posterior wall (pyloric). Rapidly spreading. Slight thickening commencing.

Case 2. F.; aged 60. **Indigestion** absent (?). **Pain** absent before perforation. **Vomiting** absent before perforation. **Rigidity** presumably absent before perforation. **Tenderness** presumably absent before perforation. **Bleeding** five years before. **Perforation** present. **Condition of ulcer**: Anterior wall (centre). Slowly spreading and healing. Slight thickening. Scars of old acute ulcers.

Case 3. F.; aged 17. **Indigestion**: Discomfort after meals for 'some time'. **Pain** absent before perforation. **Vomiting** absent before perforation. **Rigidity** presumably absent before perforation. **Tenderness** presumably absent before perforation. **Bleeding** absent. **Perforation** present. **Condition of ulcer**: Anterior wall (cardiac). Rapidly spreading. Very slight thickening. Scars of old acute ulcers.

Case 4. M.; aged 51. **Indigestion** absent. **Pain** lower abdomen, one month. Not related to meals. **Vomiting** commenced after the pain. **Rigidity**: Whole abdomen. **Tenderness** general, and especially in both iliac fossae. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Small curvature (about centre). Healing. Some thickening of edges and base.

Case 5. M.; aged 42. **Indigestion** for years. Aching pain on and off in epigastrium two hours after meals. **Pain** severe for one year. Independent of food also. **Vomited** frequently after food. **Rigidity**: Upper recti both sides. **Tenderness**: Left costal margin. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Small curvature 1½ in. from pylorus. Advanced in healing; some thickening.

Case 6. M.; aged 37. **Indigestion** two years. Slight pain in epigastrium and back one and a half hours after food. Acid and gaseous eructations. Relieved by food. Wasting. **Pain** severe for one month. **Nausea and vomiting** half an hour after meals for three months; relieved the symptoms. **Rigidity** absent. **Tenderness**: Mid-line half-way between ensiform and umbilicus and right iliac fossa. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Stomach dilated. Ulcer on posterior wall near pylorus. Advanced in healing; some thickening.

Case 7. M.; aged 53. **Indigestion** six to seven months. Slight pain or distension, and fullness in epigastrium one and a half to two hours after meals. Not relieved by food. Acid eructations. **Severe pain** seven days, epigastrium and along costal margins, two to two and a half hours after food. **Vomiting** seven days; after food; relieved pain. **Rigidity** slight, of upper recti. **Tenderness**: Centre of epigastrium. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Stomach dilated owing to kinking of pylorus. Ulcer on small curvature 1¼ in. from pylorus; spreading; some thickening.

Case 8. M.; aged 50. **Indigestion** as long as he could remember. Wasting five months. **Severe pains** five months in upper part of abdomen, more or less constant and increased by food. **Vomiting** absent. **Rigidity**: Upper recti. **Tenderness** midway between ensiform and umbilicus. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Almost whole of small curvature. Marked thickening all round. Base formed by pancreas partly. Spreading.

It is not justifiable to draw general conclusions with regard to such variable quantities as symptoms from a small number of cases, but there are one or two points of interest which appear to be established by a perusal of the table. Broadly speaking, it appears that the more recent the ulcer is, the more nearly the symptoms approximate to those of acute ulcer, whilst the older and the more thickened it is, although healing may be advanced, the more like those of chronic ulcer are its clinical manifestations. Such a conclusion seems self-evident, but it is very interesting and important that it should be shown in a series of cases known to be transitional between acute and chronic ulcer. The diagnosis of acute from chronic ulcer is extremely difficult and is only to be made in certain cases. This latter point is not surprising when it is borne in mind that all transitions as shown by these cases may exist between the two

conditions. The presence of an acute ulcer in the stomach is not necessarily associated with symptoms; in fact, it is probably the case that most acute ulcers give rise to no direct symptoms. This is certainly true in the ulcers of infective conditions. The stomach may be riddled with ulcers, and yet the patient may complain of no symptoms. There is no reason to suppose that acute simple ulcers, as commonly occurring in medical practice and in which there is no obvious infection of the body, are exceptions to this rule. My own experience in this respect entirely agrees with that of other observers. In the majority of cases the first symptom to attract attention is sudden haematemesis, and in a very small minority of cases perforation. These conditions are accidental complications of acute ulcer, so that the proportion of acute ulcers in which no symptoms occur must be considerably larger than is ordinarily thought to be the case. Pain of recent origin is only present in a small proportion of cases, and when we consider that those patients who are most liable to acute ulcer are essentially those in which gastric irritability of nervous origin, clinically expressed as pain and vomiting, is especially common, it is probable that pain directly due to the acute ulcer is present in a much smaller proportion of cases. A certain number of the patients have had the symptoms of some form of ' indigestion' for a longer or shorter time before the acute ulcer is recognized. The relation of 'indigestion' to ulcer may be threefold: (1) they may be both the result of a common cause; (2) the acute ulcer of a different origin may have developed in the subject of ' indigestion'; (3) the cause of ' indigestion' may promote the propagation of the ulcer or prevent healing.

The typical history of chronic ulcer is that of long-standing ' indigestion', with pain and vomiting either coming on in attacks with free intervals or continually present. In nearly every case of chronic ulcer pain is present. It is possible that some cases are latent and only announced by haemorrhage or perforation, but such cases are extremely rare. A glance at the list will show that the more acute the ulcer is, the more its symptoms approximate to those of acute ulcer, and the older it is and the more thickening there is present, the more its symptoms are like those of chronic ulcer. The whole question obviously resolves itself into (1) the diagnosis of the presence of ulcer, and (2) the age of that ulcer.

The factor of chronicity is the thickening; hence as soon as thickening has commenced the ulcer is becoming chronic. It is, therefore, impossible to draw a sharp line and to say that at this point the ulcer has become chronic, neither is it possible to recognize such a point clinically. All that it is permissible to say is that in most cases definite pain and other symptoms of ulcer usually only commence when a certain amount of thickening is present, which may not occur until the ulcer has attained considerable dimensions, and that they are more severe and continuous in proportion to the chronicity.

It is frequently difficult to draw a sharp distinction between the epigastric sensations of indigestion and actual pain, and moreover pain may be present in the absence of ulcer, so that there are very real difficulties in the way. But if

the observer has convinced himself that ulcer pain has been present for a few months (five or six for example) he is justified in diagnosing chronic ulcer.

The other symptoms of ulcer depend upon the pain, so that rigidity and tenderness (superficial or deep) are of little help. If the patient be examined when pain is present, or soon after an attack of pain, rigidity and tenderness are likely to be present, but if the examination be conducted when the patient has been free from pain for some time, they will be absent. The pain of a chronic ulcer always disappears with rest in bed and a simple liquid diet, unless some complication is present, and in the history of a chronic ulcer it is not uncommon for the pain to be intermittent, the free intervals amounting to weeks or even months. Whether one ulcer only has been present all the time, or whether more than one, must be judged by the length of time the patient has been absolutely free from pain. It is an exploded idea that the pain in ulcer depends upon irritation of sensory nerves in the floor of the ulcer.

It is undoubtedly a fact that the pain is commoner in proportion to the chronicity of the ulcer, and these cases bear out that statement. If the pain has been present for several weeks, the only pathological condition one can be certain of finding is a certain amount of thickening, but whether the ulcer is spreading or whether it is healing all round or in part is impossible to foretell. The attacks of pain are not related to definite spreading of the ulcer. These cases illustrate a further point of importance, namely, that the presence of haemorrhage, profuse or slight, is no indication that the ulcer will be found to be spreading, because death may occur from the opening up of a vessel in the floor of an ulcer advanced in healing.

So far as they go these cases support the view that the position of the tender point in the epigastrium is no indication of the position of the ulcer in the stomach. I shall return to this point in a future paper in which a series of chronic ulcers will be published.

An important point illustrated by these cases is the remarkable ability to heal which they exhibit, although they have spread to a considerable size and undergone thickening.

There is no need for any special method of treatment. If the patient be put to bed and fed on a graduated diet beginning with milk and raw eggs, in the vast majority of cases the symptoms disappear and healing commences. The more chronic the ulcer the more difficult is the healing process, owing, as I was able to show experimentally and as also demonstrated in these cases, to the condition of the base rather than to a fault in the mucous membrane, which, although in a condition of inflammation, is readily able to grow over the base when it presents a suitable stroma. An objection which has been raised to any close connexion between acute and chronic ulcer is the question of age and sex incidence in the two conditions.

It is considered that since acute ulcer is commonest in young women under thirty years, and that since chronic ulcer is about equal in the two sexes or perhaps a little more common in the male sex after this age, therefore the two

maladies have different origins. It is a matter of common observation that haematemesis due to clinical acute ulcer is commoner in young women than in young men, and this is borne out by post-mortem findings.

Fenwick (57) gives the proportion of female to male between the ages of ten to thirty years as 10 to 1. In the thirteen cases of acute ulcer mentioned above (p. 436) there were three females between 10 and 30 years and no males. Above the age of 30 years, however, there were six females and four males. Clinically speaking, acute ulcer is much less common in females over the age of 30 years than in younger women, so that it appears that haemorrhage from acute ulcer is easily recovered from in early female life, but is a much more fatal event when occurring in a subject of over 30 years of age. It is probably a true statement that simple acute ulcer is commoner in women than in men, that this difference is especially marked under 30 years of age, so that over this age the numbers are much more nearly equal in the two sexes. The fatality from haemorrhage is much greater over the age of 30 years in both sexes than below it. The number of cases of acute spreading ulcer quoted here is only small, but so far as they go they bear out the idea that haemorrhage is particularly fatal in a subject over the age of 30 years, and seem to indicate that there may be more tendency towards spreading and chronicity in the male over 30 years of age. According to Fenwick's statistics (58), of 59 cases of chronic ulcer, 43 were males and 16 females. At the present time acute and chronic ulcer are not separated in most statistics, so that very little information can be gained from them with regard to the occurrence of ulcers in different stages of development in persons of various ages and both sexes. Until the different types of ulcer are separated from each other and new statistics compiled on these lines, we must be content with the statements above.

When one considers that there are different forms of acute ulcer, and that probably some forms have a greater tendency to heal and others to spread ; that age and concomitant disease must influence the tendency of ulcer to heal, to spread, and to thicken; that the subjects of ulcer differ individually with regard to condition of digestion and diet ; that statistics are largely compiled from clinical material, and that the diagnosis of ulcer is very difficult, statistical objections which are raised to the connexion between acute and chronic ulcer appear to be more imaginary than real.

There is no doubt that such associated diseases as occur in the cases described here, and which have probably no direct connexion in most cases with the ulcer, nevertheless must seriously affect the fatality of the haemorrhage due to the ulcer. The amount and rapidity of formation of the secondary thickening probably depend largely upon the general condition and age of the patient.

Concluding Section.

The main object of this paper has been to show how, by the extension of an acute ulcer and the secondary inflammatory thickening which affects the same,

and is a necessary consequence of the unhealed condition of the ulcer, a chronic ulcer arises. The funnel shape of an ulcer is not due to the fact that it arises as a result of vascular occlusion ; it is merely the result of the, mode of spread of the ulcer. The spread occurs in two directions, laterally and in the depth. If lateral extension has occurred rapidly the funnel is a very shallow one, and this shape disappears when the muscular coat is destroyed, the ulcer assuming a flattened form. If extension has occurred chiefly in the depth the funnel shape is well marked and perforation soon occurs, unless there is a well-marked inflammatory reaction and thickening. Digestion of the sides of the ulcer undermines the edges, so that the flat variety acquires a raised and overhanging edge, and the funnel-shaped ulcer is converted into a globular or other irregular shaped cavity.

Chronic ulcer probably always arises in this manner, because, so far as we know at present, every initial lesion leading to ulcer is essentially acute and produces in the first instance acute ulcer. According to the nature of this initial lesion there are several different types of acute ulcer. They are all under suitable circumstances, very little understood at present, able to spread and become chronic, but there is undoubtedly one particular type of acute ulcer which most frequently undergoes these changes.

Acute ulcer, whatever its origin, tends to heal rapidly and completely within a few weeks, and perhaps there is one type which most commonly does this. Occasionally, without showing any tendency to spread, an acute ulcer may be delayed or arrested in its healing, when thickening occurs and the condition may become chronic.

One sex is more liable to be affected by a particular type of acute ulcer than the other.

The multiplicity or the reverse of the ulcers, the position in the stomach occupied by them, the sex and age of the patient most affected, the recurrence in the same individual, all vary probably according to the type of acute ulcer. For instance, an ulcer due to an acute infective condition is commonly multiple, more often affects the fundus, may occur at any age, does not recur in the same individual, and usually does not spread or become chronic if the patient survives, although there is evidence to show that it may do so. These are the general principles from which the detailed pathology of chronic ulcer must be worked out, and this can only be done by the systematic classification and study of the various forms of acute ulcer.

Finally, I wish to express my sincere thanks to my colleagues on the Medical and Surgical Staff of University College Hospital for their courtesy in allowing me free access to their cases, and for the use of their post-mortem specimens.

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ILLUSTRATIVE CASES.

Case 1.

(Hospital Register No. 1736. Autopsy No. 151. Dr. Sidney Martin.)

L. M., aged 53 years, female, housewife, was admitted to University College Hospital on June 13, 1910. She complained of pain in the head and eyes, giddiness at times, failing vision, wasting, occasional vomiting. These symptoms had been present for six months. She had been constipated for twelve months previously, but had had no other illness, nor had she suffered from indigestion. The heart was hypertrophied, the vessels thickened, and the blood pressure 220 mm. Hg. There was albuminuric retinitis and a variable amount of albumin in the urine. The teeth were in good condition, the upper ones being false. The abdomen was lax, and the right kidney palpable. There was no pain, tenderness, nor any symptom of indigestion. The vomiting occurred at any time, and was not related to food; it continued on and off till the patient's death. She gradually lost flesh, and towards the end of life Cheyne-Stokes respiration developed. On August 9 there was copious haemorrhage from the rectum, the blood being dark in colour, and partially clotted. The patient died the same day.

Autopsy. Red granular kidneys were present. The left ventricle of the heart was markedly hypertrophied and dilated, and the right ventricle was similarly affected, but to a slighter extent. The aorta was atheromatous and the aortic valves slightly thickened. The lungs were emphysematous. There was an old scar at the right apex and a red infarct in the right lower lobe. The liver showed some general fibrosis. The gall-bladder was shrunken and contained six gall-stones. The capsule of the spleen was a little thickened. The intestines contained blood but were otherwise normal. The pancreas was normal.

Stomach (Fig. 1). Two ulcers were present. The larger was situated on the small curvature, which bisected it, at a distance of 1¾ inches from the cardiac orifice. Its size was 2 inches by 1½ inches. Its base was formed of subperitoneal tissue with muscular tissue in places. At four points were the open mouths of medium-sized branches of the coronary artery. The small omentum was not thickened, nor was the peritoneal base of the ulcer, to the naked eye. The anterior edge was terraced, and sloped very gradually to the base. The mucous membrane had been destroyed over a considerable area, laying bare the

submucous tissue, and internal to this was the muscular coat of the stomach. There was no thickening of this edge. The edge of the ulcer, which was situated on the anterior wall of the stomach, was almost perpendicular, cleanly cut, and slightly raised and thickened, and, as it passed into the edge described above, was terraced. The edge of the ulcer situated on the posterior wall was raised, slightly thickened and undermined, the extreme edge being slightly inverted. The smaller ulcer was $1\frac{1}{2}$ inches by $\frac{1}{2}$ inch in size. It was situated longitudinally in a line with the larger ulcer and posterior to it, but on the posterior wall of the stomach quite close to the small curvature. It was narrow in the centre and evidently formed by two round ulcers which had joined together during their extension. To the naked eye there was no thickening in any part of this ulcer. The mucous membrane was sharply punched out at the edge, and internal to this was a narrow ring of submucous tissue surrounding the whole ulcer. The base was formed of muscular tissue hollowed out in the centre of each original ulcer, and was crossed in the middle by a raised strand of submucous tissue showing where the ulcers had joined. In the centre of the anterior portion of the ulcer was a bleeding-point. The edges of the ulcer all round were terraced, and it had the appearance of being formed by two very shallow funnel-shaped ulcers. By transmitted light the ulcers looked quite thin except along the line where the small omentum was attached to the base of the larger ulcer. There were no other ulcers in the stomach, neither were there any scars.

The microscopical examination of the smaller ulcer (Fig. 2) showed a condition of gastritis affecting the mucous membrane around the ulcer ; the round-celled infiltration was only slight, so that the glands were not separated, the lymphoid follicles were a little diffuse, and there was some dilatation of the glands and desquamation of the cells lining them. At the edge of the ulcer the glands were short and bent, and there was necrosis of their superficial ends. The submucous tissue immediately under the edge of the mucous membrane was very slightly thickened, and sloughs were separating from the inner edge of this tissue, gradually exposing the muscular coat in the base. With the exception of some infiltration with cells the remaining coats were not thickened. Sections of the anterior shallow edge of the larger ulcer, where spreading was more rapid, showed a similar condition, but the mucous membrane of the edge and for some distance into the surrounding part was in an advanced stage of disintegration. There was no thickening of the underlying submucous tissue. The thickening of the undermined and raised edge (Fig. 4) was seen to be chiefly due to the increased depth of the submucous tissue, which formed a wedge-shaped mass, the thin edge gradually fading into the normal submucous tissue. The other coats were thickened to a lesser degree. The free edges of the submucous and muscular coats were necrotic, and the undermining was obviously due to separation of this dead tissue. The surface of the base of the ulcer was also necrotic. The mucous membrane at the edge was infiltrated with cells and was not being destroyed, as shown by the fact that the extreme edge of it was fused with the submucous tissue by fibrous tissue. The submucous thickening only extended

out into the wall of the stomach for a short distance.   The more perpendicular edge (Fig. 3) of the ulcer showed the same changes, but the undermining had not gone on to such an advanced condition.

Case 2.

(Hospital Register No. 2149.   Autopsy No. 122.   Mr. Trotter.)

W. A., aged 60 years, female, was admitted to University College Hospital in the evening of August 31, 1909.   She was suffering from general peritonitis, and was considered to be in too bad a condition for operation.   She died the same evening.   She was a cook in a private house, and so far as was known had been perfectly well and not complained of indigestion ; in fact, she had cooked the dinner on the evening of August 30, and shortly afterwards was taken with a sudden severe pain in the abdomen.   Five years previously she had suffered from a violent attack of haematemesis.

Autopsy.   The body was stout.   Mitral stenosis was present, the orifice admitting the tip of one finger, the right side of the heart and the left auricle being hypertrophied and dilated.   There were some recent vegetations along the free edge of the agglutinated mitral valves.   There was brown atrophy of the cardiac muscle and atheroma at the base of the aorta and of the coronary arteries.   There was also atheroma of the abdominal aorta.   The pericardium contained an ounce of clear fluid.   The lungs were emphysematous, and the pleurae adherent at both apices.   The kidneys were small, the capsules adherent, and there were large areas of atrophy in the cortex of each, which was generally diminished and tough.   The renal arteries were thickened.   There was general peritonitis, the abdominal cavity containing about three pints of turbid fluid. The stomach and liver were adherent together by recent lymph.   The intestines were also adherent.   There was a firm and older adhesion between the anterior wall of the stomach, half-way between the pylorus and cardiac end, and the anterior wall of the abdomen.   Where this old adhesion was attached to the stomach there were some soft adhesions at one side, which readily gave way, exposing the base of an ulcer (Fig. 5).   The ulcer, whose base was thus adherent to the abdominal wall, was about the size of a threepenny piece.   One edge was raised and undermined, and the opposite edge sloping and showed signs of cicatrization.   The base of the ulcer was hollowed out, and formed of muscular tissue in part and thickened peritoneum covered with black necrotic tissue.   The base had probably been torn by the adhesion to the abdominal wall, and the aperture closed by recent adhesions.   Two oval ulcers with smooth edges, and whose bases were almost level with the mucous membrane, were situated point to point on the cardiac side of the above-mentioned ulcer, and rather nearer the greater curvature.   The mucous membrane around these oval ulcers was puckered and showed lines radiating from them.   On the pyloric side of the first ulcer the stomach was a little contracted, and there were signs of several healed superficial ulcers in this position.

The microscopical examination of the raised edge of the first ulcer (Fig. 6) showed considerable thickening of the submucous tissue with necrosis of its free end, giving rise to undermining. This excavation had extended inwards for a considerable distance, and for this reason the mucous membrane was bent down a little towards the base. The superficial muscular coat of the stomach at this point projected beyond the submucous as if it had resisted digestion longer, and there was again undermining below this, separating it from the deeper muscular layer. The mucous membrane showed advanced gastritis with some necrosis of the extreme edge. The shallow edge of the ulcer showed new gastric glands proliferating and growing over a base of fairly dense connective tissue containing some bundles of muscular fibres. At one spot the growth appeared to be delayed by the superficial necrosis of this fibrous tissue. The ulcer had evidently been originally funnel-shaped, and a further excavation of the base had converted it into a rounded cavity, the edge having stopped its lateral extension for some time. The two oval ulcers were almost healed; the mucous membrane was growing over a base of muscular tissue covered by a thin layer of granulation tissue.

Case 3.

(Hospital Register No. 2641.   Mr. Raymond Johnson.)

A. M., aged 17 years, female, laundry worker, was admitted to University College Hospital on September 10, 1910. She was suffering from general peritonitis, was operated upon, and died ten days later. Seven days before admission she awoke one morning with a dull pain in the abdomen, which was generally distributed. Two days later she commenced vomiting, but still stuck to her work (mangling). The day before admission she had a hot bath in the morning, and then the pain became more acute, but was still of the same general character. She had previously suffered from ' dyspepsia ', which she described as being ' discomfort ', in the epigastrium, but there was no vomiting and apparently no actual pain.

Autopsy. Signs of peritonitis were present. The heart, lungs, and other organs showed no disease.

Stomach. The ulcer, which had perforated, was situated on the anterior wall of the stomach, $\frac{1}{2}$ inch from the small curvature, 2 inches from the cardiac orifice, and $4\frac{3}{4}$ inches from the pylorus. It was rounded and shallow. It was about $\frac{3}{4}$ inch by $\frac{5}{8}$ inch in size. The edge situated towards the small curvature was shallow, sloping, and terraced. The mucous membrane was sharply punched out, and internal to this was a shelf of submucous tissue extending for the whole width of the ulcer. Internally again was a ridge of muscular tissue, and the base of the ulcer was formed of thickened peritoneum. The thickening appeared to be chiefly the result of the acute peritonitis resulting from the perforation. There was a large rounded perforation in the base situated nearer the opposite edge of the ulcer, which was slightly undermined (Fig. 7). There was a small

acute ulcer involving the submucous tissue on the posterior wall near the
greater curvature at the cardiac end, and near to this the scar of a healed acute
ulcer.   Another tiny scar was situated on the small curvature at about its centre.
A few scattered points of congestion and petechial haemorrhages were situated in
the pyloric region on the anterior and posterior wall around the small curvature.
Three duodenal ulcers were present—a large one, $\frac{3}{4}$ inch in diameter, reaching
to the muscular coat and situated $\frac{1}{4}$ inch from the pylorus on the posterior wall ;
and two smaller ones about $\frac{3}{4}$ inch further on in the duodenum, one on the
anterior, and the other on the posterior wall.   They were both smaller than the
first one and were healing.

The *microscopical examination* of the terraced edge showed no thickening
of the submucous tissue, nor of the muscular coat, but the peritoneum was
thickened in the base.   This thickening was apparently due to the recent
peritonitis around the perforation.   The mucous membrane was very thin,
infiltrated with cells, and the glands largely disintegrated.   The opposite
undermined edge showed considerable thickening of the submucous layer and
excavation of the same.   The muscular layer projected at the edge and was
covered with a layer of necrotic tissue.   The peritoneum was considerably
thickened, formed the base of the ulcer, and was necrotic on the surface.   The
mucous membrane showed gastritis, round-celled infiltration, diffusion of the lymph
nodules, and dilatation of many gastric glands with desquamation of the cells.
This ulcer had the shape of a very shallow funnel.   One edge was spreading more
rapidly in a lateral direction than the other, with the result that the apex of the
funnel was eccentric in situation, and the perforation which occurred at the apex
was likewise eccentric.

Case 4.

(Hospital Register No. 2953.   Autopsy No. 208.   Dr. Sidney Martin.)

J. R., aged 51 years, male, wood-cutter, was admitted to University College
Hospital on October 8, 1910.   He was complaining of pain in the stomach and of
vomiting blood.   He was unable to give a very clear account of his illness, but
it appeared that the pain commenced in the lower part of the abdomen a month
previously, and was not related to meals, but came on irregularly and gradually
disappeared.   Latterly the pain had become worse, and was continuous through-
out the day and night.   The bowels were loose to begin with, and later were
rather constipated.   He began to have a feeling of nausea and to retch, and on
October 4 he vomited about a pint of dark thick fluid.   The pain continued, and
the motions were dark-coloured until admission.   He had been in the army
five years, and had had enteric fever in India in 1879.   He took one to two pints
of ale in the day.   He had had chronic bronchitis with palpitation and shortness
of breath for nine years.   On admission he was pale, thin, and breathing rather
rapidly.   He complained of pain in the lower part of the abdomen.   The
respiratory movements of the abdomen were rather limited and the whole
abdomen was somewhat rigid.   There was considerable tenderness on light

pressure, especially in both iliac fossae. No dullness was detected. There was enlargement of the heart and aortic regurgitation. For the next three days the melaena and abdominal pain continued, and then the patient began to improve until October 15, when he collapsed, became very pale, and passed a large quantity of melaena. On the following day he had an attack of haematemesis. The melaena continued, and the patient died on October 20.

Autopsy. The stomach was distended with a large blood-clot and some blood-stained fluid. An almost circular ulcer was situated on the small curvature, which nearly bisected it, the ulcer extending rather farther on the posterior than on the anterior wall (Fig. 8). It was slightly nearer to the cardiac orifice than to the pylorus. Its longer diameter was $1\frac{3}{8}$ inches and its smaller $1\frac{1}{8}$ inches, the latter corresponding almost with the line of the small curvature. The ulcer was quite shallow, the base being formed of fibrous tissue, which apparently was filling up the cavity of the ulcer. There was no more thickening of the base than could be accounted for by the process of healing of the ulcer. The edge of the ulcer which was turned towards the pylorus was slightly overhanging and raised, and that turned towards the cardia was sloping, the mucous membrane gradually fading into the base of the ulcer. The edges were quite smooth and there was no terracing. There was the open mouth of an artery almost in the centre of the ulcer. No other ulcers or scars were present. The intestines and appendix were normal.

The microscopical examination showed that the ulcer was healing all round. Round the edge the base of the ulcer consisted of vascular granulation tissue, and was quite smooth. At the undermined edge a slight cleft was noticeable between the thickened submucous tissue and the free ends of the muscular fibres, and the submucous tissue had been hollowed out. The whole edge was covered and smoothed over with vascular granulation tissue continuous with that of the base. No sloughs nor particles of necrotic tissue could be seen. At the sloping edge the slightly thickened submucous tissue was continuous with, and level with, the granulation tissue of the base. The base of the ulcer consisted of fibrous tissue with vascular granulation tissue superficially, which had grown up during healing and was continuous with the peritoneum. The surrounding mucous membrane was in a condition of marked gastritis. The glands were separated by a cellular stroma, in some places very considerable. The glands themselves were dilated to different degrees, and often completely lined by cubical epithelium containing large accumulations of mucus. In some cases they were very short and many had completely disappeared. There were signs of proliferation of the epithelium, and at the sloping edge the mucous membrane was growing over the base in the fashion quite typical of healing. This case is a very important one, because it represents an acute ulcer which had spread in each direction, the pyloric edge having been the first to stop, and then the usual thickening and undermining occurred. Healing apparently commenced all round after the edges had become clean, and before the cardiac edge had been much thickened and excavated.

Case 5.

(Hospital Register No. 43.   Sir John Bradford.)

G. T., aged 42 years, male, outside porter, was admitted to University College Hospital on January 4, 1911. The patient had suffered from indigestion for years. His chief symptom had been a dull aching pain on and off, situated in the mid-line from the lower part of the sternum to the umbilicus. The pain came on about two hours after food, especially tea, and disappeared gradually before the next meal. He was never awakened in the night with pain. For the last year he had never been free from pain for longer than a week at a time, and the pain had been much more severe, and had come on independently of food. He had often vomited after breakfast, but never brought any blood up till January 1. He had been accustomed to drink five or six pints of ale and to smoke $\frac{3}{4}$ oz. of tobacco and ten to twenty cigarettes each day. On January 1, at 8 p.m., the patient suddenly felt ill and vomited up about a pint of dark clots of blood. He had had a meal consisting of tea, toast, and cake two hours previously. The vomiting was repeated on January 3 and 4, but smaller amounts of blood were brought up. On admission the patient was blanched. The abdomen was retracted and the upper parts of the recti rigid on both sides. There was slight tenderness along the left costal margin, but no pain except in the lower part of the abdomen on coughing. On being brought up the lift in the Hospital the patient vomited a clot of blood $3\frac{1}{2}$ by $1\frac{1}{2}$ inches in size. During the next four days blood was passed by the rectum and the patient died on January 8.

Autopsy. A large clot of blood was found, forming a complete cast of the cavity of the stomach. The stomach was distended by the clot, but not otherwise dilated. A round ulcer $\frac{1}{2}$ to $\frac{3}{4}$ inches in diameter was situated on the small curvature, which bisected it, at a distance of $1\frac{1}{2}$ inches from the pylorus. The edges of the ulcer were smooth, not undermined, very slightly raised, and descended abruptly to fuse intimately with the base. The edges were finely puckered and the surrounding mucous membrane thrown into radiating folds. The base was filled up almost level with the mucous membrane, and was formed of granulation tissue. In the centre was a bleeding vessel. The rest of the mucous membrane looked healthy and presented no further ulcers or scars. The small omentum was adherent and thickened. The wall of the stomach at the base of the ulcer was no more thickened than the formation of fibrous tissue during healing would account for. There were no other lesions of importance in the body.

The microscopical examination of the edge of the ulcer showed that the mucous membrane all round was in a condition of gastritis very similar to that of Case 4. The epithelium was rapidly proliferating and a small single layer of cells had grown over on to the base for some distance, forming a thin film (Fig. 9). The base was composed superficially of granulation tissue and in its depth of more dense fibrous tissue continuous with the peritoneum. There was

thickening of the submucous tissue for a little distance out into the stomach, and the other coats were infiltrated with cells. This ulcer had spread for a certain distance all round, and then commenced to heal rapidly, and at the time of examination was in an advanced condition of cicatrization.

Case 6.

(Hospital Register No. 1567.   Dr. Risien Russell.)

B. R., aged 37 years, male, tailor, was admitted to University College Hospital on May 28, 1910. The patient had been ill for two years with 'indigestion'. He had had slight pain in the upper part of the abdomen, below the umbilicus, and between the shoulders, which came on $1\frac{1}{2}$ hours after a heavy meal, but not if the patient lived on eggs and fish. The pain came on about every two days and was sometimes absent for a month. He also had eructations of acid fluid and gas, appearing at the same time as the pain. The above symptoms were relieved by food. For the last three months the patient had had nausea and vomiting, which came on especially after the midday meal, and relieved the symptoms. He never vomited blood nor passed black motions. The pain had become much worse during the past month and he had vomited every day about half an hour after food. He had wasted considerably, his appetite was good, and the bowels constipated. The abdomen was lax and its walls thin. Slight tenderness was present on deep palpation in the mid-line half-way between the ensiform cartilage and the umbilicus, and another spot of tenderness was situated midway between the latter and the right anterior superior iliac spine. No tumour was present. The stomach was found to be dilated on physical examination, and a bismuth meal of bread and milk passed out of the organ more slowly than normal, a considerable amount being still present after six hours, showing motor insufficiency of the stomach. Examination of the stomach contents showed a total acidity of 0·3285 per cent., and the total HCl secreted 0·281 per cent. The patient rapidly improved, lost his symptoms, and after the expiration of three weeks a gastro-enterostomy was performed because of the motor delay and dilatation. The patient died the next day, and since a full autopsy was not permitted the cause of death was not known.

Examination of stomach. The stomach was dilated, but there was no stenosis of the pylorus. The duodenum was normal. On the posterior wall of the stomach, about 1 inch from the pylorus, was situated a healing ulcer. It was oval in shape and about $\frac{1}{2}$ in. by $\frac{1}{4}$ in. in size. Its position was transverse, one end being near the small curvature. It was quite shallow, the granulation tissue forming the base being quite clean, and having grown up level with the mucous membrane. The edges of the ulcer all round were sloping and slightly puckered, and the mucous membrane gradually became thinner and thinner as it faded away into the base of the ulcer. The peritoneum corresponding with

the base of the ulcer was opaque and thickened and a few peritoneal adhesions were present.

Microscopical examination. The mucous membrane in the vicinity was thin and showed marked changes of gastritis. At the edge of the ulcer proliferation was taking place, and the epithelium was growing over the base all round the ulcer. The muscular coat had been perforated over a small area in the centre of the ulcer, and the gap was filled up with fibrous tissue continuous with the peritoneum, which was thickened over a somewhat larger area. The submucous coat was much thickened at the edge of the ulcer and for about a quarter of an inch outside this. The base was completely filled up with granulation tissue. The acute ulcer had not spread to any great size, no undermining of the thickened submucosa had occurred, and healing had commenced very promptly.

Case 7.

(Hospital Register No. 3860.   Autopsy No. 4.   Dr. Risien Russell.)

F. C., aged 53 years, male, violin-maker, was admitted to University College Hospital on December 25, 1910. He had had syphilis twenty years before. He took a pint of beer a day and occasionally spirits. For the past six or seven months the patient had suffered from indigestion. His symptoms were pain, which he said was not severe, and was better described as a feeling of great distension or fullness, most marked in the epigastrium, and which came on $1\frac{1}{2}$ to 2 hours after meals. This feeling used to pass off gradually and was not relieved by taking food. He had acid eructations but no vomiting. His appetite was always good, and he lived on a fairly ordinary diet with perhaps rather less meat than is usually taken. Seven days before admission he commenced to feel definite pain in the epigastrium, which radiated outwards on both sides along the costal margin. This pain was only present after food and came on about 2 to $2\frac{1}{2}$ hours after eating. The pain was relieved by vomiting, which now commenced. On December 20 patient felt faint and brought up about a teacupful of blood brownish in colour. On three later occasions the attack of haematemesis was repeated, the blood being similar in amount and bright red. On admission the patient, a well-nourished man, was pale and restless. His abdomen was somewhat retracted but moved well all over. There was very slight deep tenderness in the centre of the epigastrium, but no superficial hyperasthesia, and slight rigidity of the upper recti. He continued to pass melaena for the two following days. After this he became delirious and the heart began to fail. His general condition was very bad, and he developed retention of urine and died on January 4, 1911.

Autopsy. The stomach was dilated and distended with gas. It contained a small amount of brownish fluid with small black flakes. On the small curvature, and bisected by it, was a shallow oval ulcer, which extended for about equal distances on the anterior and posterior surfaces of the stomach.

Its long axis was situated tranversely. The size of the ulcer was $2\frac{3}{4}$ by $1\frac{1}{2}$ inches and it was situated $1\frac{1}{4}$ inches from the pylorus. There were inflammatory changes in the small omentum, which had contracted adhesions to the gall-bladder and first part of the duodenum. The adhesions were firm, but there was not much thickening. By this means the small curvature of the stomach was somewhat contracted and the pyloric orifice kinked. This had no doubt caused the dilatation of the stomach. The edge of the ulcer turned towards the pylorus was elevated a little and overhanging. It passed gradually into a sloping, almost flat edge, which was turned towards the cardia. The base of the ulcer was not thickened appreciably and was formed of omental and subperitoneal tissue. Around the edge could be seen in places the remains of the muscular coat of the stomach and one part of the sloping edge was definitely terraced. The open orifices of two arteries could be seen in the posterior base of the ulcer. On the posterior wall of the stomach were several superficial ulcers running in a line parallel to the great curvature, their surfaces being black or red. The duodenum was normal. The other organs showed no noteworthy change except some oedema and hyperaemia of the bases of the lungs, and some fatty change in the liver.

Microscopical examination. The raised and undermined edge of the ulcer showed considerable thickening of the submucous tissue, which extended out into the wall of the stomach for some little distance. The muscular coat at this point was about twice its normal thickness, and this thickening was not due to infiltration with cells but to retraction of the muscular fibres. The submucous tissue had been hollowed out into the form of a cleft, and the mucous membrane and underlying submucous tissue had collapsed on to the muscular coat. The peritoneal coat was thickened at this spot. The undermining of the edge was seen to be due to the separation of necrotic portions of the submucous and muscular layers as in the previous cases. There was no attempt at healing and the base was covered with necrotic tissue. The mucous membrane itself showed the changes of gastritis of the same type as Case 4. Sections of the sloping edge showed the mucous membrane in a condition of disintegration. The mucous membrane was thin and infiltrated with cells. The glands were short and often dilated into globular spaces, with disintegration of the epithelium lining them, and in places they had disappeared, although leaving only strands of interstitial tissue with round-celled infiltration and groups of gland cells in places. The submucous tissue was considerably thickened here, and became continuous with the thickened peritoneum, the ends of the muscular fibres losing themselves in the fibrous tissue.

Case 8.

(Hospital Register No. 1312.   Autopsy No. 94.   Sir Thomas Barlow, Bart.)

This case is one of definite chronic ulcer, and it is introduced here because all the changes which have occurred in it are so precisely like those of the

foregoing cases that it is impossible to believe that it had any other origin than an acute one.

A. L., aged 50 years, male, painter, was admitted to University College Hospital on May 5, 1910. He had suffered from 'indigestion' as long as he could remember, and had had painter's colic two or three times. For the past five months he had had severe pain in the upper part of the abdomen, which was increased by food. He had had no vomiting, but had been wasting and growing weaker during this time. For the last week his motions had been dark in colour. He was in the habit of taking three or four pints of ale a day. On admission he was seen to be extremely pale and wasted. He was constantly wriggling and tossing about in bed and rubbing his legs together, and seemed quite unable to keep still. He also complained very much of feeling cold. It was impossible to obtain any further history from him than the above. The tongue was very dry and the teeth much decayed. There was a slight indication of a blue line on the gums. There was diffuse pulsation over the upper part of the abdomen and tenderness in the epigastrium midway between the umbilicus and ensiform cartilage. Both recti were a little rigid in the upper part. The liver was felt just below the costal margin. On the following day the patient passed some melaena. He remained very restless and slept badly, and on May 9 his breathing became rapid, his heart began to fail, and he died the next morning.

Autopsy. The stomach was dilated. A round ulcer, 2 inches in diameter, was situated on the small curvature which bisected it (Fig. 10). The ulcer extended equally on the anterior and posterior surfaces of the stomach, and was about an inch distant from the pylorus and a similar distance from the cardia, the small curvature being contracted. The ulcer was shallow. The wall of the stomach around the ulcer and extending outwards for 2 inches or more was thickened, stiff, and adherent to the neighbouring structures. The base of the ulcer in places was nodular from the presence of lobules of the pancreas, the surface of which formed the base of the ulcer, and projected into the stomach. The orifices of two small arteries appeared in the base of the ulcer. The small omentum was thickened and adherent, and several enlarged lymphatic glands were found. The edge of the ulcer which was turned to the pylorus was hard and raised. It was also undermined. This undermining of the edge extended round on to the anterior and posterior surfaces of the stomach, and on the anterior surface, especially, large sloughs could be seen to be separating from the edge under the mucous membrane, by the separation of which the latter would become overhanging. The edge of the ulcer turned towards the cardia was very sloping; in fact, the surface of the mucous membrane passed insensibly into that of the base. Sloughs, quite thin and superficial, could be seen separating from the submucous layer internal to the edge of the mucous membrane, and in places at this edge the muscular coat of the stomach appeared on the surface. No other ulcers or scars were to be seen on the mucous membrane. The muscular substance of the heart was pale and soft and showed

areas of marked fatty change, especially in the columnar and papillary muscles. The liver was also a little fatty and the kidneys showed early granular change. The vessels were not thickened.   There were no other noteworthy changes to be found in the body.

Microscopical examination.   The mucous membrane around the ulcer showed a marked condition of gastritis.   The interstitial tissue was densely infiltrated with cells, and the glands were separated to a considerable extent. They were also considerably dilated and many had been destroyed.   The submucous tissue was enormously thickened all round the ulcer, and this thickening extended out for about two inches into the surrounding wall of the stomach.   The peritoneal coat was also thickened markedly, especially at the edge of the ulcer, but not to the extent seen in the submucous layer.   The muscular coat was cut up by, and embedded in the fibrous tissue, but could be recognized up to the edge of the ulcer, and at the sloping edge it came to the surface internal to the thickened submucous layer, the ends of the fibres turning up towards the surface.   At the overhanging edge the submucous and other layers forming the side of the ulcer had been excavated by the separation of sloughs, and the mucous membrane at its free edge was turned down and curved backwards so that the extreme edge of the mucous membrane almost touched the base (Fig. 11). This process of excavation could be followed perfectly in places, as large sloughs were actually in process of separation (Fig. 12).   Sloughs were also peeling off the submucous layer at the sloping edge.   Here the mucous membrane showed both destructive and proliferative changes, and at one spot the epithelium was actually growing up to the edge of a patch of necrosed tissue.   The base of the ulcer was formed of dense fibrous tissue, with fat and lobules of the pancreas embedded in it, and there was necrosis of the superficial layers with the separation of tiny sloughs.

DESCRIPTION OF FIGURES.

PLATE 23, FIG. 1.   Photograph of the ulcers of Case 1.   The lower ulcer is formed of two acute spreading ulcers which have united, the original line of division being represented by a strand of submucous tissue.   Each original ulcer is of a very shallow funnel shape.   The edge is terraced and the base formed of muscular tissue, hollowed out in the centre.   The large upper ulcer shows an acute spreading edge, which is terraced, at the upper left-hand corner. The lower left-hand edge is raised and undermined, and the right edge is almost vertically cut and raised.

FIG. 2.   Photograph of a section of the edge of the lower ulcer in Fig. 1.   The section shows slight thickening of the submucous tissue of the edge of the ulcer.   On the left-hand side of the section a slough is seen to be separating from the submucous tissue.   The muscular coat of the stomach is exposed by this means and terracing of the edge of the ulcer produced.

FIG. 3.   Photograph of a section of the right edge of the upper ulcer in Fig. 1.   The submucous tissue at the edge is considerably thickened and necrotic at its free end.   The edge of the underlying muscular coat is also necrotic and the latter is also somewhat thickened. Undermining has not yet appeared.

PLATE 24, FIG. 4.   Photograph of a section of the undermined edge of the upper ulcer in Fig. 1.   The wedge-shaped thickening of the submucous tissue is well seen, and also the undermining of the edge by the separation of necrotic tissue.

FIG. 5.   Photograph of the stomach of Case 2.   Towards the upper edge of the specimen is a small ulcer, the lower edge of which is undermined and raised and the upper edge sloping and partially cicatrized.   The two oval ulcers to the right are almost healed.   On the left-hand side in a corresponding situation the mucous membrane is superficially scarred.

FIG. 6.   Photograph of a section of the undermined edge of the upper ulcer in Fig. 5. There is thickening of the submucous tissue and also of the peritoneum.   The undermining is due to the separation of sloughs from the side of the ulcer and not to retraction of the muscular coat, which is projecting into the cavity of the ulcer.

FIG. 7.   Photograph of the stomach of Case 3.   The lower edge of the perforated ulcer is shallow and terraced, and the opposite edge a little thickened and undermined, and towards this side is situated the perforation.   The three duodenal ulcers are easily distinguished. The photograph is rather too small to show the other lesions in the stomach.

PLATE 25, FIG. 8.   Photograph of the ulcer of Case 4.   The edges of the ulcer are quite smooth all round.   The upper edge is undermined and clean ; the lower edge sloping but not terraced.   On section the ulcer is seen to be filling up all round with granulation tissue and the epithelium growing inwards over the base.

FIG. 9.   Photograph of a section of the edge of the ulcer of Case 5.   The whole base is composed of granulation tissue, and a single layer of epithelial cells can be seen growing over the base from the mucous membrane of the edge of the ulcer.

FIG. 10.   Photograph of the ulcer of Case 8.   Both cardiac and pyloric orifices are visible and the ulcer occupies a large part of the small curvature.   Lobules of the pancreas are showing through in the base.   The pyloric edge is undermined, and the cardiac shelving and becoming terraced by the separation of thin sloughs.   This terracing can be seen better on section, as it is masked by the great thickening of the wall of the stomach.   At the edge of the ulcer on the anterior wall large sloughs are separating and causing undermining of this edge.

PLATE 26, FIG. 11.   Photograph of the undermined edge of the ulcer in Fig. 10.   Enormous thickening of the submucous tissue is seen, and also of the peritoneum.   The undermining has been produced by separation of sloughs from the sides of the ulcer.

FIG. 12.   Photograph of a section of the right edge of the ulcer in Fig. 10.   A large slough is in process of separation, which will lead to undermining of the edge.
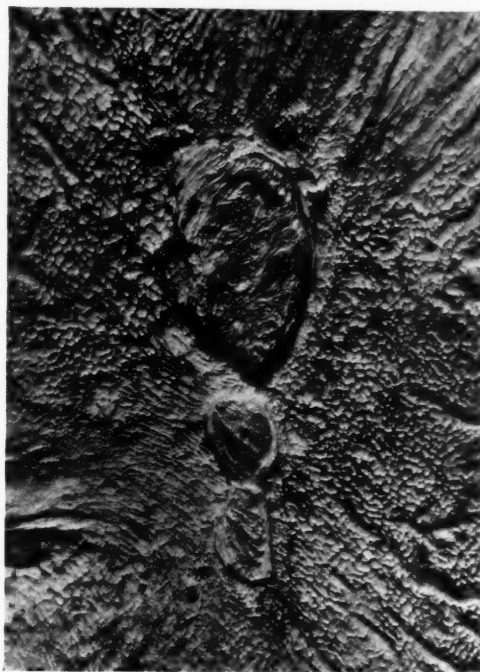
Fig. 1
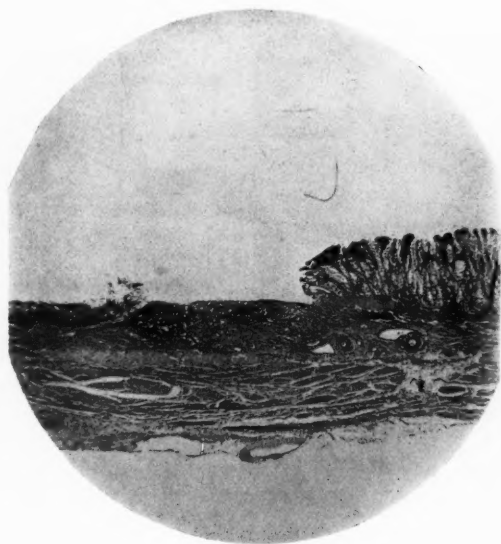
Fig. 2

Fig. 3

Fig. 4
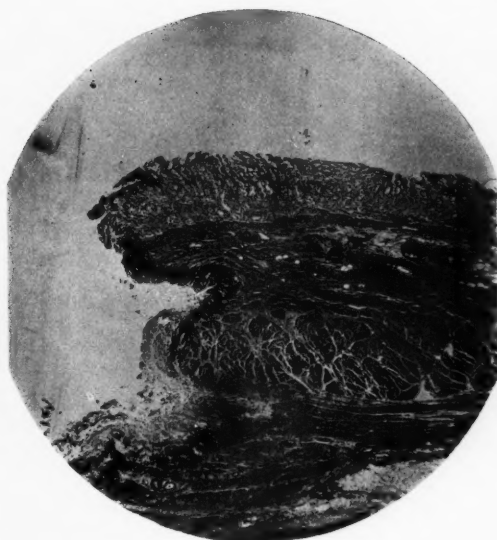
Fig. 6
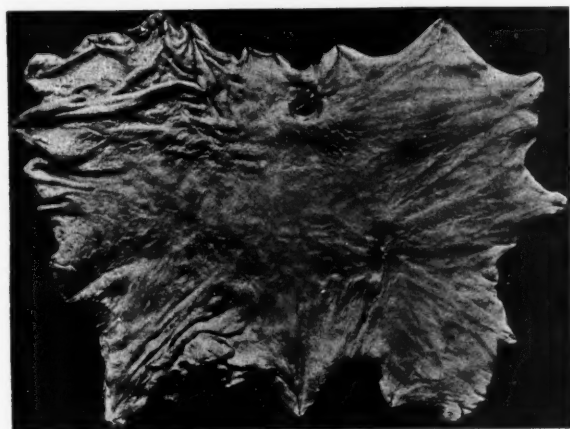
Fig. 5
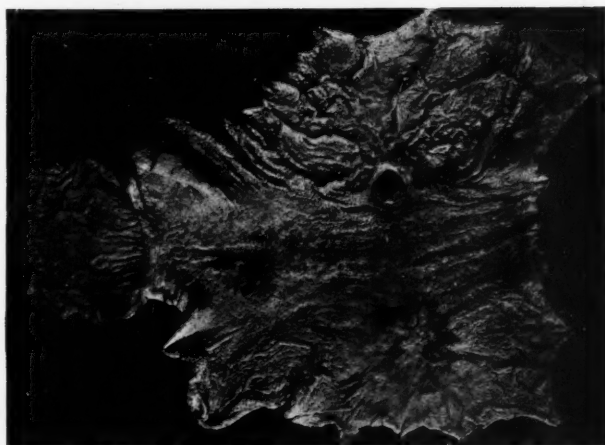
Fig. 7
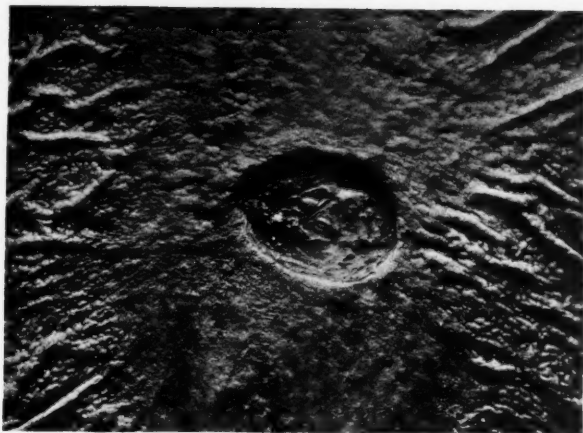
FIG. 8

FIG. 9

FIG. 10

Fig. 11

Fig. 12

A RESEARCH UPON COMBINED MITRAL AND AORTIC DISEASE OF RHEUMATIC ORIGIN. A CONTRIBUTION TO THE STUDY OF RHEUMATIC MALIGNANT ENDOCARDITIS

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With Plates 27–29

Section I.

(a) *Object of the communication.* We return in this investigation to the consideration of the second statement that we made in our paper upon the causation of acute rheumatism published in the *Lancet* in September, 1900. This statement was to the effect that *acute rheumatism produces a malignant as well as a simple endocarditis.*

At the outset we would insist upon the exact wording of this assertion in order to avoid the mistake being made that we are thought to maintain that rheumatism is the only cause of this condition.

It has been repeatedly proved that there are many causes of malignant endocarditis, and we would venture to make the generalization that any infection which attacks the valves of the heart may produce this lesion, and to express our belief that when an infection which only produces endocarditis exceptionally does happen to attack the valves then the malignant form of endocarditis is prone to result.

On many previous occasions we have commented upon the peculiar attitude that has been adopted to rheumatism, in that it has been almost universally taught that it is a cause of simple or healing endocarditis, but needs the assistance of a secondary infection to produce the malignant form. Surely this is a curious example of seeking a difficult path, when the plain and easy one lies before us.

In this paper we are approaching our subject from a somewhat different point of view to that from which we dealt with it in a former paper ('A contribution to the study of malignant endocarditis,' *Medico-Chirurgical Transactions,* Vol. 85, 1903), for we are here studying a form of heart disease which we believe every one must allow may be the result of the rheumatic infection itself and not of any added infection.

In the course of this communication we shall quote from our former paper which established certain facts that may be lawfully utilized to illustrate our present contention, which is to this effect: *That from a study of severe heart*

*disease of rheumatic origin involving lesions to two important valves, we find
all gradations between simple and malignant endocarditis, and additional and
striking proof of the existence of a malignant rheumatic endocarditis.*

We would also add, in opposition to a statement by Horder[1] to the effect
that the original distinction between non-infective and infective as applied to
endocarditis may be allowed to remain, that such a division is in our opinion
a survival of an obsolete pathology only supported by imperfect investigations
and conceptions, and as such is a hindrance to advance in the study of heart
disease.

(*b*) *Acute rheumatism a specific disease.* We are desirous at this point of
dealing with a criticism of our investigations which has been frequently repeated,
and has been recently made again at a meeting of the Pathological Section of
the Royal Society of Medicine in March, 1912. It is one to this effect, that
we assume the fact that there is a specific disease, acute rheumatism. It is
impossible for any but skilful speakers to answer such a criticism as this in
a short debate, but we are prepared to put in writing the reasons for our con-
tentions, to which we firmly adhere and by the truth or falsity of which we are
prepared to stand or fall.

The question is one the answer to which necessarily brings us in contact
with fundamental conceptions of human disease, and we would urge at once
that diseases such as acute rheumatism are not and never will be conditions that
can be pigeon-holed into compartments with rigid walls. The farthest one can
see clearly concerning such a problem is this: That certain pathological pro-
cesses may produce results in the human body, which, when they prove fatal,
can be studied sufficiently thoroughly, sufficiently accurately, and sufficiently
frequently to permit the statement that they clinically and pathologically
present a process of disease unlike any other. Such a disease we hold must be
built up upon the study of fatal cases, although it may be frequently delimited
at the bed-side when not fatal.

It is not in our opinion any scientific objection to the view that we put
forward for a critic to quote a case which has been thought by many doctors to
be acute rheumatism and yet has proved to be of a different nature because, for
example, a staphylococcus has been isolated and the patient cured by a vaccine!
What scientific weight can such a statement as that possibly have? We should
be the first to allow that we have made and shall make errors in the clinical
diagnosis of acute rheumatism, and that other diseases may resemble it very
closely. We do not suppose acute rheumatism is the only cause of a transient
polyarthritis in man; or that it is the only disease that produces heart affections,
or even arthritis and heart disease combined. Twelve years ago we were con-
versant with these cardinal difficulties in the study of acute rheumatism which
from time to time are presented to us by critics as though they were new
suggestions. We have, indeed, ourselves pointed out that some cases of infection
that result from middle ear disease are almost impossible to distinguish from

[1] *Quarterly Journal of Medicine,* ii. 290.

acute rheumatism. Yet no one would attempt to study any disease by the uncertain light of exceptional cases, for such a procedure would be foredoomed to failure, and it is essential, we think, in studying acute rheumatism to investigate the classical examples of which in our Hospital note-books there are ample records.

The first step that we have believed essential for establishing the specific nature of this disease has been to study side by side post-mortem records and clinical histories of acute rheumatism. In this way we have obtained not only the results of our own experience, but the independent observations of many different skilled physicians and pathologists. The remarkable records at the Hospital for Sick Children, Great Ormond Street, alone contain upwards of 200 fatal cases, and in addition to this we have many examples in older subjects recorded in recent years at St. Mary's Hospital and University College Hospital. Further, we have investigated microscopically on many occasions the important cardinal lesions and the exudations of the disease. Lastly, we have investigated the bacteriology in nearly 100 cases, and studied the experimental lesions.

The outcome of these investigations has been that we hold that there is decisive evidence from clinical and pathological observations of fatal cases that acute rheumatism is one of the most special of diseases in this country—a view we believe to be supported by nearly every physician of eminence who has studied in a Children's Hospital. Evidence such as this is not to be lightly set aside by the relation of unusual cases, or of cases unsupported by accurate clinical and post-mortem investigations.

It is as the infective agent of this specific disease that we claim the diplococcus, and would add that the statement made by critics that various bacteria have been isolated from cases of rheumatism should carry now no real weight. The only evidence we hold that can be now admitted as worthy of consideration is that which brings with it the proof that these various bacteria have not only been isolated, but have reproduced the lesions of the disease, as has the diplococcus. Those who maintain that the cause of the disease is still unknown should in all fairness now, after a period of at least ten years has elapsed, during which positive results have been obtained by others, justify their cause by some slight positive contribution of their own to our knowledge.

In a recent and admirable review of the study of rheumatism during the last decade by Sanderson,[2] our position and that of others who support our views has been described as becoming more isolated. Even if we admit this—which we do not—we would venture to ask of the impartial looker-on, whether scientific inquiry is to be measured by the number of investigators or by the character of the results? As far as acute rheumatism is concerned, with the increasingly isolated group of investigators remain such results as the demonstration of experimental arthritis both acute and chronic, endocarditis simple and malignant, pericarditis, myocarditis, pleurisy, peritonitis, pneumonia, nodule

[2] *Guy's Hospital Reports*, 1911, p. 193.

formations, appendicitis, choreiform movements, large white kidney, and infarctions—all obtained by a micrococcus isolated from the cardinal lesions of acute rheumatism, and most of them previously quite unknown in the experience of pathologists in this country.

Various Types of Rheumatic Infection.

If acute rheumatism is a specific disease, the result of infection with a diplococcus of the streptococcal group, what clinical types of the disease may be reasonably expected to be met with ? The answer to this question has important bearing upon our investigation of 100 cases of mitral and aortic disease of rheumatic origin, for we wish to show that this infection is not extraordinary in its behaviour but quite in accord with what may be reasonably expected of such a condition.

Firstly, it may produce a more or less general infection and damage many organs. Sometimes it does this very acutely, but more frequently with a moderate degree of severity. In this group will be found, as is the case with other infections, many examples in childhood. In such, mitral and aortic disease is only one incident, and there are in our list classical examples of such cases which have proved fatal.

Secondly, the severity of the infection may fall on certain organs, notably the heart, or even upon certain parts of the heart, for example the valves.

These lesions may heal and leave scars which in the case of valvular lesions may introduce a new train of symptoms the results of mechanical heart disease. In our list there are convincing examples of this occurrence.

Again, the lesions may heal, or rather let us add appear to heal, almost entirely and yet exacerbate, or arise anew as a result of fresh activity, with the result that we find after death evidences of scarring and activity combined. Thus, thirdly, the active lesions in the valves in such cases may be only incidents in a but renewed general infection, or, fourthly, they may, as we shall hope to show, be the cause of death by a virulence and activity which are recognized under the name of malignant endocarditis.

Fifthly, from the first the endocardial lesions may show this malignancy and be the cause of death.

Such various results of infection as these are in no way remarkable; indeed, as we have previously stated, it would be much more remarkable if they did not occur.

Sixthly, it is only to be expected that in a long series of cases of mitral and aortic disease examples will occur which are exceedingly difficult to group. The result is we arrive at the conclusion that as a consequence of the rheumatic infection we may find every grade, from a primary malignant endocarditis to long healed lesions, which have caused death, not from any active process but entirely from a mechanical disability of the circulatory apparatus, the result of the scarred and deformed valves.

*Necessity for considering Mitral and Aortic Disease in Rheumatism as
an Event in the History of an Infective Process.*

There are few physicians who have not been struck with the paralysing effect of nomenclature in the study of disease.   We have here, we think, a very good example of such an occurrence.   In looking through records it is brought home to us that a condition such as combined mitral and aortic disease of rheumatic origin is repeatedly looked upon as an example of 'heart disease'. We must emphasize that for our purpose such a conception is practically useless, and moreover it is frequently not correct.   The condition is undoubtedly in a sense one of heart disease, and when these lesions represent the scars of some long dead infection such a description is correct, but when, as reference to our list of cases will at once make clear, there are not only valvular lesions but active valvular disease, the condition is not one of heart disease but of active heart disease; that is, it is a phase in the life-history of a prolonged infective process. Our paper rests in great part on this study of these valvular lesions as active events in acute rheumatism, and we shall endeavour to place them in the picture of a rheumatic infection, and not to isolate them under the benumbing title of heart disease.

The combined lesion can be produced experimentally both as the result of a single and of a repeated infection, and in some instances the involvement of the two valves has appeared to be the result of a direct spread of the infection from one valve to the other, the segments being in very close proximity.   The usual sequence on account of the greater frequency of mitral disease is for he aortic valve to be affected the later of the two, but we would not deny the possibility of the reverse occurrence, although up to the present we have had no experimental proof in its support.

At the bed-side also we find the two lesions appearing in various ways. Sometimes the aortic disease follows rapidly upon the mitral during a prolonged attack of endocarditis.   Sometimes after a pause in the activity of the infection, but before the patient is well enough to leave bed, there is a definite recrudescence with the appearance of an aortic lesion.   Again, aortic disease may arise in a subsequent attack, and then it is very difficult to decide whether it is an independent infection of the valve by rheumatism or whether it is that this lesion is recognized by the appearance of new clinical signs, but its origin in reality is a spread from the older mitral endocarditis which has simultaneously reawakened to activity.   Lastly, the aortic lesion may be the first event, although this is a less frequent occurrence.

The combination of valvular disease is of interest because it shows that in the young mitral regurgitation due to relative incompetence of an undamaged valve is decidedly rare as a result of aortic regurgitation, for in such case there is almost invariably active disease of the mitral valve also.   It is, however, of far greater interest because it suggests *the dawning of a malignant tendency in the endocarditis.*   We believe also that in man, as in animals, there may be

a direct spread of infection from one valve to the other, and that when this is the case we have one of the great features of the malignant type. In the post-mortem records of malignant endocarditis emphasis is invariably laid upon the spread of vegetations to the heart wall, to the chordae tendineae, to the musculi papillares, or the wall of the aorta. A direct spread from one valve to another in immediate proximity in no way differs from these occurrences.

The clinical study of rheumatic mitral and aortic disease illustrates well that behaviour of the rheumatic infection in the tissues which we have already foreshadowed.

Thus, first, the valvular lesions may be but one incident in a fatal general infection, as for example in the case of a boy aged 4½ years, who died in a first attack of acute rheumatism after twelve weeks' illness. During life there were polyarthritis, nodules, and aortic and mitral disease with peri-carditis. After death, subacute pericarditis was demonstrated with acute mitral and aortic endocarditis. In such cases we are dealing with acute rheumatism invading many tissues.

In the second place, the endocardial lesions may completely heal and the patient die of cardiac disabilities (asystole), aortic or mitral in type, in accord with the predominance of the particular lesion.

Thus, for example, a man aged 42, who had suffered repeatedly from acute rheumatism, came under observation for mitral and aortic disease with dyspnoea and repeated attacks of angina pectoris. There was no fever and death was sudden. The necropsy showed thickened aortic and mitral valves with atheroma of the aorta. There was no active disease, and the course of the case was aortic in character.

Again, a man aged 50, who had suffered from acute rheumatism at 8, 25, 36, and 49 years, had been failing for many weeks with progressive dyspnoea, dropsy, and the other signs of mitral asystole. There was aortic and mitral disease and death ensued. The necropsy showed mitral stenosis with shortening of the chordae tendineae, and calcification of both mitral and aortic valves, proof of a dead infection. The last illness had been afebrile.

Thirdly, death may occur in a recurrent attack of a more or less general rheumatic infection in which once more the valvular lesions are but an incident, but in which after death both recent and old injuries are demonstrable.

Thus, for example, a boy aged 10 years, who had suffered from acute rheumatism at 6, had been ill for twelve weeks before death. During this last illness there had been pericarditis, arthritis, and nodules, and there was also aortic and mitral disease. The necropsy showed recent pericarditis and thickened aortic and mitral valves with, in addition, recent vegetations.

Fourthly, the disease of the valves may in a subsequent attack become the salient feature of the illness and show that persistence and virulence which is described as malignant. Thus, a boy aged 13 years, who had acute rheumatism with severe carditis at 10, was under observation for twenty-four weeks with peri-carditis which subsided, and aortic and mitral disease which steadily progressed,

accompanied by high fever and embolisms. The necropsy showed a recently adherent pericardium and malignant endocarditis of both aortic and mitral valves.

Fifthly, from the first the valvular disease may be malignant in type, as in the case of a boy aged 7 years whose sister and mother were the subjects of acute rheumatism, and who himself in an illness of four weeks developed first a polyarthritis, then a rheumatic erythema, and then pericarditis. The necropsy showed recent pericarditis, malignant mitral and simple aortic endocarditis.

Sixthly and lastly, every sort of transitional case may occur, of which we will give three examples :—

(i) A boy aged 16 years, who had suffered from attacks of acute rheumatism at 6, 8, 10, and 12 years, was under observation in his final illness of eight weeks. During this period he developed a polyarthritis which subsided, and the combined valvular lesion with which he was already crippled steadily progressed with high fever and embolisms. During life, and after death, the case was described as a malignant endocarditis, but the vegetations upon the aortic and mitral valves were pointed out as small and resembling those of rheumatic endocarditis.

(ii) A man aged 19 years had suffered from acute rheumatism at 11, 14, 17, and 18. Since the last attack his health had been failing for months, and a sore throat had preceded his final breakdown. Under observation his temperature never rose above 99·5° F., and when sudden death occurred the natural diagnosis was 'heart disease'. The post-mortem examinations showed a calcified mass on the aortic valve with malignant vegetations around it, and malignant endocarditis of the mitral valve.

(iii) The third case is a clinical example only. A male aged 38, who had previously suffered from three attacks of acute rheumatism, was under observation with the combined valvular lesion and cerebral embolism. For six weeks there was persistent fever with gradual asystole, but eventually there followed a slow and partial recovery, the temperature quieting down and the signs of hemiplegia improving. Such a case would be difficult to place with any confidence either as a simple or a malignant type of endocarditis.

This brief outline of salient examples brings us to the end of the introductory division of this paper, for we know that there will be no dispute as to the nature of the first three types we have exemplified, but that over the last three classes, namely the malignant cases supervening on old rheumatic endocarditis, the primarily malignant ones, and the transitional cases, there will be dissension of opinion, and it is these cases that bring to a focus the main issue of this contribution.

In the next section we shall frequently use the term malignant rheumatic endocarditis, but we do not use it, as Horder asserts ought to be done, as connoting rheumatism complicated by streptococcal or other infections of the endocardium. According to this writer, the name is only 'permissible' in that sense; we would, however, modify this statement of his, and we would state that the name malignant rheumatic endocarditis is only permissible when it is used to express the fact that the diplococcal rheumatic infection may produce a malignant endocarditis.

<p style="text-align:center">SECTION II.</p>

<p style="text-align:center">I. *The Establishment of a Working Basis for the Thesis.*</p>

It appears to us that the most simple and direct method of presenting our facts is to give first of all examples of rheumatism with mitral and aortic disease which we hold to establish the following claims : 1. That acute rheumatism may cause aortic and mitral endocarditis. 2. That this endocarditis may eventually prove malignant, although coincident with the appearance of this malignancy other non-malignant or simple manifestations of acute rheumatism may appear and quiet down. 3. That the endocarditis in these malignant cases is caused by a strepto-diplococcus indistinguishable from that obtained from simple rheumatic endocarditis. 4. That this strepto-diplococcus will produce in animals on intravenous injection both simple carditis and malignant endocarditis.

Case I. A boy, aged 10 years, was admitted suffering from active heart disease. Twelve months before he had had a severe attack of acute rheumatism, during which both the mitral and aortic valves were damaged. His final illness had commenced six weeks before, with breathlessness, anaemia, and wasting, and shortly after admission pericarditis developed. Two weeks later arthritis of the ankles and knees appeared. There seemed very good reason to look upon this condition as the result of another attack of severe rheumatism, a view favoured by the disappearance of the pericarditis and arthritis. In spite, however, of these signs of improvement the temperature remained high and the child lost ground. The explanation that now seemed feasible was that there was an unusually intractable simple endocarditis in progress, but during the next two months infarctions, sweating, anaemia, and fever pointed to the condition as malignant. Death occurred from sudden heart failure.

The necropsy demonstrated a generally adherent pericardium of recent date, the subsidence of all arthritis, extensive malignant endocarditis of the aortic and mitral valves, and renal and splenic infarctions.

A pure growth of strepto-diplococci was obtained from the valves, indistinguishable from that we have isolated from simple rheumatism. The first rabbit intravenously injected developed polyarthritis and malignant endocarditis of the *aortic and mitral valves.* The diplococcus was recovered in pure culture. The second developed malignant aortic endocarditis ; the third, polyarthritis and simple cardiac dilatation ; the fourth, malignant mitral endocarditis ; the fifth, general pericarditis and polyarthritis ; the sixth, polyarthritis only.

It appears to us that this case illustrates the four points we have put forward as rigid tests of our contention. We have the rheumatic origin of the lesion, the non-malignant evidences of active rheumatism during the final illness, and the complete experimental chain of evidence.

The next case (Case II) is not quite so complete because of the absence of a multiple arthritis during the final illness.

Case II. A boy, aged 13 years, had suffered from severe rheumatic fever at the age of 10, leaving him with mitral and aortic disease. For two months previous to his coming under observation he had been ill with precordial pain, dyspnoea, anaemia, and wasting. He was evidently suffering from active carditis, and succumbed after an illness of four months. Throughout the whole of this time there was irregular fever, and there was considerable enlargement of the spleen with other signs of a progressive endocarditis.

The necropsy showed general and recent pericardial adhesions, malignant aortic and mitral endocarditis, and a large spleen with infarctions.

A pure growth of strepto-diplococci was obtained. The first rabbit injected developed a mitral murmur for a while and eventually died many weeks afterwards—when no lesion was forthcoming. No. 2 died of malignant mitral endocarditis with infarctions. No. 3 died with simple mitral endocarditis and dilatation. No. 4 died of fibrinoplastic pericarditis. No. 5 died with general recent adhesion of the pericardium.

II. *Histological Support.*

For many years emphasis has been laid upon the frequency of a history of a previous attack of rheumatic fever in cases of malignant endocarditis, and it is this that has led to the suggestion that antecedent damage to the valves favours the development of the malignant endocarditis.

With this view we are in agreement, but our explanation differs very distinctly from that usually accepted. First of all, however, we would point out that those who have opposed our views upon acute rheumatism have strangely neglected to publish and show any microscopical studies of the valvular lesions of rheumatism and malignant endocarditis in their various phases in man and animals. Yet this omission is, we think, a serious defect in their case, for in experimental endocarditis it is possible to trace every step from the earliest invasion of the valvular tissues to the exuberant malignant vegetation, and in human endocarditis to study nearly every phase of simple and malignant endocarditis and the methods of their healing.

If rheumatic endocarditis is not infective in origin it is remarkable that its lesions are indistinguishable from those of an infective process. If, on the other hand, it is the result of some unknown infection it is interesting to find that microscopy is unable to distinguish between the nature of the results produced by this infection and the malignant endocarditis that may occur in the rheumatic.

It is also interesting to find that in the malignant form numerous strepto-diplococci can be demonstrated in the vegetations and are generally admitted to be the cause of the lesion, but that in simple endocarditis, in which the strepto-diplococci can also be demonstrated—though in scanty numbers, for simple endocarditis does not kill—the causal nature of these bacteria is brushed aside. This is the more remarkable when it is pointed out that the experimental lesions of simple and malignant endocarditis, when obviously caused in both instances by the diplococcus isolated from the human lesions, show the same variation in the number of diplococci in accord with their nature, a point we demonstrated to the Pathological Society of London in 1900.

Although there may be difficulty in isolating the diplococcus from rheumatic lesions, a fact which has been forced upon us, we may add rather to our surprise, through the reports of other pathologists, we can hardly think that there can be any justification for a failure to demonstrate diplococci in acute simple rheumatic endocardial lesions. This is but a matter of accurate technique and sufficient

diligence, and that this may not seem a boast, we will support it by a quotation from a recent paper in *Heart* by H. G. Butterfield, Graham Research Scholar in University College Hospital Medical School. This writer, undertaking an entirely independent research upon acute carditis and heart-block, of which we were quite unaware, reports thus on the mitral valve of a case of classical rheumatic carditis :

'Bacteriological examination showed the presence of numerous Gram-positive diplococci with a tendency to short chain formation and in some cases to only partial retention of the methyl violet stain used. Some of these organisms were very small, and in general they were smaller than the ordinary streptococcus pyogenes.' In our first paper we pointed out the minute size of the streptococcus and its only relative Gram-staining properties in tissues.

We may add that since seeing his sections we asked him to be good enough to undertake the examination of another classical case in which Graham Forbes had isolated the micrococcus from the pericardial exudation. In this he demonstrated the diplococci in the lesions of acute rheumatic pericarditis.

Why deny the causal agency of these micrococci in the simple lesions and accept it in the malignant, in the face of the positive experimental results that have been published and specimens of which may be seen by any interested person in the Hunterian Museum ?

There is, however, another point that is established by microscopy, which is that in the partially healed lesion of rheumatic endocarditis foci of necrotic tissue are found shut off by fibrous tissue or by proliferating tissue cells.

These foci we look upon as areas of danger in which the micrococci may long exist in a latent state. Further, it is, we believe, certain both from pathological study and clinical investigation that the vegetations often described in rheumatism as recent may have been of long standing. Even in a case of fatal carditis where there was much thickening and fibrous change in the mitral valve, we found on section that within the fibrous tissue there were still areas of necrotic tissue present. In such an occurrence there is nothing remarkable when it is remembered that sometimes rheumatic nodules may remain for many months, and that a section through the centre of one of these will show necrotic tissue ; and also that in chronic pericarditis the same phenomena can be demonstrated.

The examination of malignant vegetations throws very interesting light on the sequence of events. We need not delay by dwelling upon the well-known fact that in the most active part of the vegetations thousands of diplococci will be found. The point of importance is that in many of the slow cases there are well-marked attempts at cure in the vegetation, and if this process is studied we find that the necrotic areas become less filled with clearly staining micrococci and numerous refringent granules become visible. These are soon extremely difficult to differentiate from the groundwork in which they lie, and at last an area is reached where it is difficult to decide whether the necrotic tissue does or does not contain micrococci. The alteration in the staining properties of these micrococci in rheumatic endocarditis is deserving of close attention, and

we are surprised that our opponents have never commented upon this point, which has such a close bearing upon the presence or absence of micrococci in this condition. Now if we turn for a moment to a study of some phenomena *in vitro* we find some suggestive points. The micrococcus of rheumatism does not thrive on agar-agar—a fact repeatedly ignored. If, however, we sow from this poor culture on to a mixture of bouillon, lactic acid, and milk, and the growth recovers sufficiently to clot the milk, we find that on examination of the amorphous clot numerous micrococci are beginning to appear. At first it is difficult to be sure whether one is looking at milk clot or micrococci, later the micrococci take the stain well, and later still they form obvious chains. This reverse process is very suggestive and leads us to believe that the necrotic tissue in damaged valves may contain micrococci much more frequently than is thought.

Our interpretation of the tendency for malignant endocarditis to occur in damaged valves is, then, that circumstances of increased virulence arise and latent micrococci *in* the valves produce this change in the lesion. This inception of a new virulence is not peculiar to the rheumatic infection.

Even these results of microscopy do not exhaust the valuable assistance that can be obtained from this branch of inquiry, and we must confess to a slight feeling of injustice when a distinguished pathologist at a public meeting criticized our investigations as largely dependent upon cultures from the throat, which, he maintained, were open to the most serious error.

Such cultures undoubtedly are, and our work in this direction was not attempted until we had isolated the micrococcus from all the important lesions and studied it by experiment in culture and in the human and animal tissues. The last points brought out by a study of the microscopy are these: that in some cases of very acute simple rheumatic endocarditis, such as occur, for example, in rare cases of fatal chorea, the vegetations, although minute, contain within them vast numbers of the micrococci. Such a section is indistinguishable from that through a malignant vegetation, and we have shown such examples on more than one occasion. Again, it is not rare to find in a fatal malignant endocarditis of the aortic and mitral valves simple vegetations upon one and malignant upon the other. On this account we have maintained that the essence of malignancy is not the size of the vegetations but the number and relative virulence of the micrococci, a statement borne out by the undoubted fact to be recognized in our series, that a case which has been diagnosed as malignant may at the necropsy only show minute vegetations.

III. *Support from Blood Cultures.*

We must now turn to the results of blood cultures which are taken during life in cases of acute rheumatism and malignant endocarditis. These have in our opinion been made responsible for statements which appear to us hardly justified by facts, for they require a very open-minded consideration of the pathological processes in acute rheumatism. To us the actual results that are obtained, far

from militating against the view we hold upon the causation, lend distinct support. If we interpret the reasoning of our opponents aright it is as follows: In many cases of malignant endocarditis a streptococcus is obtained by blood cultures, but in simple acute rheumatism the results are negative, therefore malignant endocarditis in the rheumatic is an epiphenomenon. We cannot accept these premisses or their interpretation. First let us ask the unbiased inquirer to picture the exact nature of the processes in acute rheumatism and we will postulate the original infection as tonsillar in origin. There is at once a gap in our knowledge which is not likely to be easily bridged over, and that is any idea of the number of micrococci which gain access to the blood stream. It is conceivable in the predisposed that a small infection only is requisite, and that this original supply multiplies in the local lesions. We do not yet know the number of micrococci that are sufficient in such people to produce a definite lesion; probably they are very few. This, however, is clear, that acute rheumatism consists of a number of *local foci* of infection in the tissues, and is not a general septicaemia. Further, there is great resistance to the disease, and the bacteria are rapidly destroyed in the blood and in these tissues. Now this being the case, it seems to us exceedingly unlikely that the withdrawal upon one or two occasions of some 5–10 c.c. of blood from the general circulation is going to yield a positive result. Why should it? If such an event were the rule we certainly should need to recast the pathology of this infection. Nevertheless in very severe and virulent cases with many grave lesions and evidences of systemic poisoning a positive result might be obtained. This is precisely our own experience, for all the cases of acute rheumatism in which we have succeeded have been of that type. Thus, for example, a girl aged 17, the victim of chorea at 12, and rheumatic fever at 15 years of age, was seized with acute illness commencing with sore throat, multiple arthritis, and purpura. She was admitted under Dr. D. B. Lees for fever, multiple arthritis, severe purpura, and general carditis, pericardial friction appearing eight days after admission. Venesection was ordered on two occasions, and on both a pure culture of strepto-diplococci was obtained. Three months later the patient had so far improved as to be allowed on a couch, but asystole gradually developed and death ensued.

The post-mortem examination showed recent pericardial adhesions; the mitral aortic and tricuspid valves were all thickened, but there were no recent vegetations, still less evidences of malignant endocarditis, recent or old. The cause of death was myocardial disease from the severe carditis.

Here is proof that during the acute course of a severe rheumatic fever strepto-diplococci can be isolated from the circulation, and incidentally conclusive evidence that such a result was not due to agonal infection. This result is one of very real importance, for it disproves the loose statement that is sometimes heard, that the isolation of bacteria from the blood in active heart disease is proof of malignant endocarditis.

We must add, though it is perhaps obvious, that to look upon a positive

culture of streptococci from the blood in a case of malignant endocarditis as evidence that the infection is not rheumatic is, in our opinion, quite unjustifiable.

The rheumatic diplococcus in fluid media tends to become streptococcal in character, and believing, as we do, in a rheumatic malignant endocarditis we should expect a streptococcus might be obtained in such cases. We would venture to add that the great majority of investigations in this country upon malignant endocarditis stop short of throwing any real light upon the essential point in dispute, for they almost always end either with the statement that a streptococcus was isolated, or with some primitive remarks upon the morphology, which we look upon as valueless, as we note also does Beattie, or with an attempt at classification by some laboratory tests *in vitro* which we and others cannot accept. What more, it may be fairly asked, would we demand? Our answer is, a careful series of experimental and histological investigations. If as a result of these both malignant endocarditis and simple rheumatism result, the answer can be given as nearly as is possible in the present stage of our knowledge. Experimental proofs far outweigh in our opinion tests *in vitro*.

We have had other cases of acute rheumatism which have recovered and from which we have isolated the diplococcus from the blood stream, but this one, from the fact that there was a necropsy, stands out as a clear proof of the nature of illness.

When we have a malignant endocarditis in rheumatism we have an unusual situation to deal with, in that there is then a focus teeming with micrococci actually impinging on the general circulation. Under such circumstances it is only to be expected that blood culture will prove to be positive in a far greater proportion of attempts, and if such were not the case we should have also to recast our views upon the pathology of this affection. Yet even in these circumstances, if the disease is of low virulence and the blood examination be made early, repeated negative results may be obtained by skilled bacteriologists—an event which is again only to be expected, but does not justify the assertion that the case is not malignant.

It is clear that we differ in one important respect from our opponents upon this question of blood culture, for we dispute the statement that results in *acute* rheumatism are *always* negative.

IV. *Additional Evidence from a Study of the Series of* 100 *Cases.*

We believe now that we have reasonably established a claim to adopt this attitude toward cases of malignant endocarditis which are associated with previous acute rheumatism or which commence as attacks of rheumatism, viz. that the onus of proof that such are not rheumatic rests with those who deny that such a condition exists.

It must not be expected that in this series of 100 examples of mitral and aortic cases from various sources complete chains of evidence are to be forth-

coming, seeing that few physicians look upon the malignant types from our point of view, and that no bacteriologist, unless devoting himself to such a special study, will be likely to have made more than the routine investigation of the blood or vegetations. Then again, in the non-malignant cases the lesions have often been considered as examples of heart disease and no particular stress laid upon them as phases in a prolonged rheumatic infection. Our evidence must then be of necessity fragmentary, but it is lawful for us, we think, to build up our thesis upon the carefully prepared basis of our complete investigations—that is, upon the four claims set out at the beginning of this section, strengthening the position by the aid of numerous other important fragments of evidence. It remains for any opponent to demolish the structure by bringing forward equally clear evidence that cases of this type are due to some other cause which is clearly of a different nature to the one we claim.

In order to avoid any suspicion that we are now trying to evade a plain issue, we will illustrate the character of our evidence by concrete examples of malignant endocarditis. The first case we quote is for the purpose of showing that we have weighed our evidence in every incomplete case.

A child, aged 4 years, had been ill ten days with arthritis of the shoulder, hips, and wrist joints; high fever and mitral disease. Pneumonic signs developed and death occurred.

In our opinion, if we published such a case as this as an example of a virulent first attack of rheumatism we should deserve the most drastic criticism.

The necropsy showed periostitis of the right femur, multiple suppurative arthritis, suppurative pericarditis, abscesses in the muscles, and early mitral disease. The *Staphylococcus pyogenes aureus* was isolated and was the cause of the illness.

On the other hand, a girl aged 11 had an attack of acute rheumatism at 9 and again at 10 years. Her final illness showed active carditis with persistent fever; no infarctions were observed. A strepto-diplococcus was isolated from the blood and at the necropsy malignant aortic disease was discovered with acute mitral of the simple type. Both valves showed former disease. The other viscera accorded with the diagnosis of a rheumatic infection. Such a case we claim to be rheumatic, until others can bring more convincing evidence to the contrary.

There is a very close clinical and pathological similarity in many of these cases of malignant endocarditis which becomes apparent from the short details of twenty-five examples that occurred in our series, and we feel justified in claiming some cases upon such clinical or clinical and pathological evidence, admitting at once that the proof is not complete, but believing the explanation as by far the most probable.

Case I. A man aged 27 years had chorea as a boy, and an attack of rheumatic fever at 26. He never laid up during the attack, but struggled on with his work, gradually losing ground. Compelled at last to give in, nine months after the neglected illness, he was found to have aortic and mitral

disease with fever and died in under a fortnight. The necropsy showed malignant aortic and mitral disease and evidences of previous cardiac rheumatism.

This case we would explain as a rheumatic malignant endocarditis, probably produced by neglect of the acute rheumatism, an explanation which would necessarily fail if opponents can produce a series of examples of such cases for which a better solution can be given. We think that in this case also the endocarditis had probably been active the entire nine months and was only under observation in the terminal phase.

Case II. The next case, which is of interest as an aortic and mitral one that cannot be included in our series, illustrates the difficulties that have to be encountered in any attempt at the study of disease in man, and to which we are fully alive.

A woman, aged 28, had suffered from rheumatic carditis after scarlet fever as a child and had never been well since her confinement thirteen months before. At the time of her confinement there was fever. After ten weeks of acute illness with purpura, paroxysmal fever, multiple embolisms, and progressive weakness she succumbed. No organism was isolated. The necropsy showed large vegetations, some with calcareous deposits in them, on the aortic valve and the anterior flap of the mitral. There were no abscesses, but white infarcts. Those who claim that this was a secondary infection of septic nature dating from the confinement have as strong evidence in their favour as those who would suggest that there was a lurking rheumatic endocarditis, which, in the puerperal state, awoke to virulence. The data are therefore insufficient and the case valueless on this account.

There is another difficulty to be faced over the determination of the nature of a carditis which is from the first malignant and is apparently the solitary lesion, or almost so. No one disputes the occurrence of a primary simple rheumatic endocarditis, that is, a pure cardiac rheumatism—and we naturally go a step further and ask, if this is admitted, why deny the possibility of the same, but in a malignant form, occurring in a first attack of rheumatism? Experiment proves that the rheumatic organism can produce malignant endocarditis in a previously healthy valve.

Example I. Thus, for example, a child of fourteen years who gave no history of previous illness was seized with a sudden hemiplegia. There were irregular fever and wasting for seven weeks, and evidence of mitral disease. Blood culture was negative. Malignant mitral endocarditis and old mitral disease were present with infarctions.

This was not a mitral and aortic case, but even if it had been we should not have included it in our series for lack of data. Nevertheless, it is most probable that this was an example of malignant rheumatic endocarditis.

Example II. The ground is far safer in the following example, already quoted in the first section, of a boy aged 7 years, whose mother and sister were the subjects of acute rheumatism, and who himself in an illness of four weeks developed polyarthritis, a rheumatic erythema, and then fatal pancarditis. Simple aortic and malignant mitral disease were found with pericarditis and the strepto-diplococcus isolated. In this case we have other manifestations of acute rheumatism. Such a case we look upon as undoubtedly rheumatic and as a link with that group which for the present purpose we may call transitional, in that they are clinically on the border line between simple and obviously malignant rheumatic endocarditis.

Example III.   Again, a girl of nine years had been ill four months with moderate and persistent fever.   Polyarthritis had developed early in the illness and passed off; then severe mitral and aortic disease developed, with an enlarged spleen and multiple embolisms.   After death, malignant aortic and mitral endocarditis was present.

We are quite aware, as one of the cases we have chosen has illustrated, that a polyarthritis in a child need not be rheumatic.   A transient affection of the joints such as occurred in the above case is, however, much more suggestive of acute rheumatism than any other disease.   When a series of cases of this kind is studied and all the evidence we have put forward deliberately weighed, we believe that we are justified in asking that those who dispute the nature of such an arthritis and endocarditis should produce definite facts in support of their contention, and not generalize from the well-known fact that there are many causes of arthritis.

We repeat that the preceding cases have been quoted in order to show that now that we are dealing with examples of malignant endocarditis which have not been completely investigated we have not assumed that they are necessarily rheumatic, but have balanced the evidence both for and against this view.   The appended list from our series given in brief will enable the reader to form his own opinion upon the value of our evidence.   We may add that nine examples of malignant endocarditis have been excluded because they were obviously the result of other infections, and fifteen were of uncertain nature and open to grave criticism.

It is very interesting to find in the list below all grades of virulence in the rheumatic process, and there are some cases which lead us to the next group.   This is, we admit, quite an artificial one and called by us transitional because it bridges over the gap between the certainly malignant and the third group, which contains examples of acute rheumatism showing damage to the mitral and aortic valves of the simple type.   As we pass to the transitional group the conclusive evidence becomes more and more difficult to obtain, because recovery is more likely to occur, and among these examples it may well have been that some were in reality of the malignant type and others of the simple. It is, if our view is correct, much more scientific to abandon these two terms simple and malignant and to substitute for them active rheumatic endocarditis. Such a term is much more satisfactory from every point of view, for it is less alarming to the patient; it represents more accurately the true pathology and in no way blinds our eyes to the meaning of this activity when it reaches the degree in which the embolic phenomena and consequent systemic poisoning show that life is clearly threatened.   Possibly the objection may be raised that such a condition of malignancy is utterly unlike any other manifestation in rheumatism, but we would point out that no other severe lesion in this disease could run a parallel course, however malignant it might be, for no other rheumatic lesion stands in the same relation to the general blood stream.

There is a statement that has been made about the relation of an attack of malignant endocarditis to previous rheumatic heart disease which we would

traverse as a very misleading one. It is to the effect that the two conditions, though associated, are as a rule quite independent of one another. Our series shows that there may be every variety of relation from immediate to remote, and we would add that because the relation is a remote one it is no proof at all that the malignant process is non-rheumatic. If any statement can be made about such cases it would be that the final condition, other things being equal, is more likely to be rheumatic than the result of any other infection.

Analysis of 100 *Cases of Rheumatic Aortic and Mitral Disease.*

At this point, before we give the first table of cases illustrating rheumatic mitral and aortic lesions, it will be convenient to give a brief analysis of the complete series of 100.

1. *Sex.* 51 were females and 49 males.

2. The age incidence was as follows :

1–10 years	15 per cent.
11–20 ,,	32 ,, ,,
21–30 ,,	23 ,, ,,
31–40 ,,	15 ,, ,,
41–50 ,,	10 ,, ,,
51–60 ,,	3 ,, ,,
61–70 ,,	1 ,, ,,
71–80 ,,	1 ,, ,,

3. *Clinical groups.*

I. Cases developing from the first or in subsequent attacks malignant endocarditis, 25.

II. Cases on the border line between malignant and simple endocarditis, at least 13.

III. Cases illustrating acute rheumatic simple endocarditis, either as an incident in a widespread infection or as the predominant lesion, 33.

IV. Cases illustrating mechanical disabilities from the results of scarred valves :

A. Symptoms chiefly aortic : 7 cases.

B. Symptoms chiefly mitral : 22 cases.

4. *Fatal cases.*

44 cases were fatal—and some of the others who left the hospitals were taken away on account of their hopeless condition.

23 of the 25 examples of malignant endocarditis in Group I succumbed, and the remaining 2 only returned home in a dying condition.

4 of the 13 cases in Group II were fatal, but this group is an artificial one, made for the purpose of exposition, and is not to be looked upon as an entity.

11 of the 33 in Group III were fatal.

6 (2 in Group A and 4 in Group B) were fatal of the 29 cases in Group IV.

5. Bacteriological evidence is necessarily incomplete, for in the majority of cases none was made. 12 positive results were obtained in the 25 malignant cases and 6 were reported negative. The comparative success in this group is entirely in accord with the view of the pathology we have put forward.

Negative results in the simple rheumatic cases (Group III) are the rule, but there are exceptions. We would repeat that a single or even two such examinations of the blood are but little evidence of the presence or absence of an infective process when the result is negative, and that in our opinion far too much weight has been laid upon the occurrence of these negative results when the morbid processes in acute rheumatism are thoroughly realized.

6. The relation of the final illness, when fatal, to the last attack of rheumatism can be readily studied from our lists. The facts thus obtained are only relative, for, when a patient has been the victim of repeated attacks of acute rheumatism, the more closely the history is investigated the more frequently will be found evidence of some activity of the rheumatic processes between the definite attacks: these minor attacks are frequently not recorded and not mentioned by the patients.

7. All the observations upon the duration of the illness are also only approximate, but they serve to illustrate how prolonged the illness may be and how difficult it is to ascertain the commencement or the end of the active processes.

8. We would lay special stress upon the following histories from the groups of the malignant cases. First, three in which the malignant process dated from the first illness; two in which it followed upon an attack of rheumatism six months before, from which illnesses the patients had never really recovered; one in which there was a continuous history of failing health for twelve months after the fourth attack of acute rheumatism; one in which the patient neglected a previous attack of rheumatism which had occurred less than a year before and after which he had been ill fed and had kept at work; one in which there had been failing health following a rheumatic polyarthritis five months previously.

These 8 cases out of a series of 25 show the close relationship of the rheumatic process to malignant endocarditis. 9 more illustrate the malignant endocarditis emerging from other and transitory symptoms of acute rheumatism. Thus 17 of these 25 cases show a close relationship to the occurrence of acute rheumatism.

GROUP No. I.

Mitral and Aortic Cases Malignant in Type.

No. 1. Male, aged 10. **History of acute rheumatism** at 9 years. **Main symptoms of final illness:** Admitted with mitral and aortic disease—developed transient polyarthritis and pericarditis. Later infarctions, persistent fever, &c. **Approximate duration:** 18 weeks. **Bacteriology:** Strepto-diplococcus isolated from valves. **Result:** *Death.* Malignant mitral and aortic, recent pericardial adhesion, white infarctions in spleen and kidneys.

No. 2. Male, aged 13. **History of acute rheumatism** at 10 years. **Main symptoms of final illness:** Mitral and aortic disease, transient pericarditis. Infarctions and persistent

high fever. **Approximate duration**: 24 weeks. **Bacteriology**: Strepto-diplococcus isolated from valves. **Result**: *Death.* Malignant mitral and aortic, recent and old pericarditis, infarctions.

No. 3. Male, aged 16. **History of acute rheumatism** at 6, 8, 10, and 12 years. **Main symptoms of final illness**: Mitral and aortic disease, transient polyarthritis, fever, infarctions. **Approximate duration**: 8 weeks. **Bacteriology**: Strepto-diplococcus isolated. **Result**: *Death.* Malignant in the clinical course and in the post-mortem evidence of infarctions, but the vegetations on the two valves resembled those of *severe simple endocarditis.*

No. 4. Female, aged 37. **History of acute rheumatism** at 23 years. **Main symptoms of final illness**: Polyarthritis (subsiding), aortic and mitral disease, enlarged spleen, high fever, progressive course. **Approximate duration**: 18 weeks. **Bacteriology**: Strepto-diplococcus isolated from blood stream. **Result**: *Death.* Simple aortic endocarditis. Malignant mitral. Infarctions in the spleen.

No. 5. Male, aged 7. **History of acute rheumatism**: First attack. **Main symptoms of final illness**: Polyarthritis, pericarditis, erythema multiforme, acute aortic and mitral disease, high fever. **Approximate duration**: 4 weeks. **Bacteriology**: Strepto-diplococcus from pericardial fluid. **Result**: *Death.* Sero-fibrinous pericarditis, acute simple aortic malignant mitral endocarditis.

No. 6. Female, aged 14. **History of acute rheumatism** at 12 and 13 years. **Main symptoms of final illness**: Transient polyarthritis, mitral and aortic disease with continuous fever, evidences of infarction and nephritis. **Approximate duration**: 6 weeks. **Bacteriology**: Negative. **Result**: *Death.* The endocarditis was in character of the simple type; the lesions *qua* infarctions and nephritis, and the clinical course, were of the malignant type.

No. 7. Female, aged 21. **History of chorea** at 7 years; **acute rheumatism** at 20 years. **Main symptoms of final illness**: Mitral and aortic disease with irregular fever, infarctions, and nephritis. **Approximate duration**: 16 weeks. **Bacteriology**: No report. **Result**: *Death.* Malignant type of vegetations on the mitral valve. On the aortic and tricuspid valves small vegetations.

No. 8. Female, aged 37. **History of acute rheumatism** as a child and 6 months before final illness. **Main symptoms of final illness**: This illness imperceptibly followed upon an attack of rheumatic arthritis 6 months before. There were aortic and mitral disease. Moderate intermittent fever and infarction. **Approximate duration**: Gradual; probably 6 months. **Bacteriology**: Negative. **Result**: *Death.* Malignant endocarditis of the mitral and aortic valves with infarctions in spleen.

No. 9. Male, aged 19. **History of acute rheumatism** at 11, 14, 17, and 18 years. **Main symptoms of final illness**: This patient had never recovered from his last attack of acute rheumatism, but his symptoms increased after a sore throat, being those of mitral and aortic disease with slight fever never above 99·5° F. Sudden death occurred and the case was not suspected to be malignant. **Approximate duration**: Gradual over 12 months. **Bacteriology**: None made. **Result**: *Death.* Malignant mitral endocarditis recent and some vegetations on the aortic segments which were thickened and calcified.

No. 10. Male, aged 50. **History of acute rheumatism** at 42 years. **Main symptoms of final illness**: An illness of some months' duration with transient polyarthritis in the articulations of the fingers. Aortic and mitral disease, later infarctions and purpura. The pyrexia persistent but at first mild, gradually increased in severity. **Approximate duration**: Some months. **Bacteriology**: Strepto-diplococcus from the circulation. **Result**: *Death.* Malignant endocarditis of the mitral, aortic, and tricuspid valves.

No. 11. Female, aged 16. **History of acute rheumatism** at 12 years. **Main symptoms of final illness**: A long illness with polyarthritis, persistent fever, aortic and mitral disease, and infarctions. **Approximate duration**: 14 weeks. **Bacteriology**: Strepto-diplococcus from the circulation. **Result**: *Death.* No necropsy, but a case of the malignant type.

No. 12. Female, aged 11. **History of acute rheumatism** at 9 and 10 years. **Main symptoms of final illness**: A comparatively rapid case in which there was high fever and severe aortic and mitral disease. **Approximate duration**: 7 weeks. **Bacteriology**: Strepto-

diplococcus isolated from circulation. **Result**: *Death*. Small vegetations on the mitral, malignant on the aortic valve. No infarctions.

No. 13. Male, aged 27. **History of chorea** as a boy; **acute rheumatism** at 26 years. **Main symptoms of final illness**: During the attack of acute rheumatism at 26 the patient would not rest but persisted with his work—steadily losing ground with cardiac symptoms until within 10 days of his death. During this time there was fever with severe mitral and aortic disease. **Approximate duration**: About 9 months; 10 days' acute illness. **Bacteriology**: None made. **Result**: *Death*. Malignant aortic and mitral endocarditis.

No. 14. Female, aged 16. **History of acute rheumatism** at 12 years. **Main symptoms of final illness**: Admitted with multiple arthritis, which subsided, and also mitral and aortic disease. For some 3 months there was high fever. The spleen enlarged and was tender. **Approximate duration**: About 12 weeks. **Bacteriology**: None made. **Result**: *Death*. No post-mortem.

No. 15. Male, aged 11. **History of acute rheumatism** at $7\frac{1}{2}$ years. **Main symptoms of final illness**: A case of progressive mitral and aortic disease—pericarditis with transient polyarthritis, infarctions, enlarged spleen, and irregular fever. **Approximate duration**: 11 weeks. **Bacteriology**: Strepto-diplococcus from blood stream. **Result**: *Death*. Recent pericarditis. Malignant mitral and small aortic vegetations.

No. 16. Male, aged 13. **History of acute rheumatism** at 7 years. **Main symptoms of final illness**: A case of progressive mitral and aortic disease with irregular fever and infarctions. **Approximate duration**: 17 weeks. **Bacteriology**: Negative. **Result**: *Death*. Aortic malignant vegetations, mitral small vegetations.

No. 17. Female, aged 9. **History of acute rheumatism**: First attack. **Main symptoms of final illness**: Admitted with multiple arthritis and mitral and aortic disease; there was moderate irregular fever throughout. The spleen enlarged, and emboli occurred, finally cerebral haemorrhage. **Approximate duration**: 16 weeks. **Bacteriology**: None made. **Result**: *Death*. Malignant aortic and mitral endocarditis.

No. 18. Female, aged 8. **History of acute rheumatism**: First attack. **Main symptoms of final illness**: Ill for 3 weeks with acute heart disease. **Approximate duration**: 3 weeks. **Bacteriology**: Strepto-diplococcus from aortic valve. **Result**: *Death*. Recent small vegetations on mitral and tricuspid, larger on aortic.

No. 19. Female, aged 17. **History of chorea and morbus cordis** at 12 years; **acute rheumatism** at 15 years. **Main symptoms of final illness**: An acute illness with typhoidal character of fever, commencing with a stiff neck. Delirium, purpura, and infarctions followed mitral and aortic disease. **Approximate duration**: 4 weeks. **Bacteriology**: Strepto-diplococci from blood stream. **Result**: *Death*. Extensive mitral malignant endocarditis spreading on the anterior flap of mitral and the neighbouring aortic cusp. Infarctions in spleen and kidneys.

No. 20. Female, aged 24. **History of chorea** at 8, 13, and 15 years. **Main symptoms of final illness**: Six months previously acute rheumatic arthritis, since then never well, severe aortic and mitral disease—persistent irregular fever, infarctions in spleen and kidneys. **Approximate duration**: 8 weeks. **Bacteriology**: Strepto-diplococcus from blood. **Result**: *Death*. No post-mortem.

No. 21. Female, aged 48. **History of acute rheumatism** at 38 years. **Main symptoms of final illness**: Failing health for 12 months—signs of cardiac asystole with irregular fever and aortic and mitral disease. **Approximate duration**: Gradual. **Bacteriology**: None. **Result**: *Death*. Malignant endocarditis, aortic and mitral.

No. 22. Male, aged 28. **History of acute rheumatism** at 18 years and minor attacks since. **Main symptoms of final illness**: Acute illness—typhoidal in character, high fever, aortic and mitral disease with multiple embolism. **Approximate duration**: 6 days' acute illness. **Bacteriology**: None. **Result**: *Death*. Malignant aortic and mitral disease.

No. 23. Female, aged 27. **History of acute rheumatism** at 13 and 17 years. **Main symptoms of final illness**: Failing health for 8 months with moderate irregular fever. Aortic and mitral disease and renal and splenic infarctions. **Approximate duration**: 5 weeks' acute illness. **Bacteriology**: Negative. **Result**: *Death*. No post-mortem.

No. 24. Female, aged 12. **History of acute rheumatism** at 7 years. **Main symptoms**

of final illness: Mitral disease, later developed aortic regurgitation with high irregular fever and haematuria. **Approximate duration**: 10 weeks. **Bacteriology**: Negative. **Result**: Left with the diagnosis of malignant endocarditis.

No. 25. Female, aged 32. **History of acute rheumatism and chorea** as a child. **Main symptoms of final illness**: 5 months' history of pains in the joints and limbs, 6 months under observation with irregular fever, aortic and mitral disease, pallor and emaciation. **Approximate duration**: 11 months. **Bacteriology**: Negative. **Result**: Left with active fever thought to be malignant.

GROUP II.

Transitional Cases.

When experimental endocarditis is produced with the diplococcus, whether isolated from a simple or malignant rheumatic endocarditis, every grade of severity may result. Recovery may occur or speedy death, and vegetations of all sizes may develop. It is impossible when dealing with this experimental endocarditis to justify the use of the terms 'simple' and 'malignant', and it is evident enough that the particular result is a question of the virulence of the cardiac infection. If this is the case with a small animal such as a rabbit whose cardiac valves are so minute and whose resistance is so comparatively weak, it is much more evident in man, in whom the resistance to the rheumatic infection is so considerable and in whom the infection we can hardly believe occurs in such a gross fashion as by the method of intravenous inoculation. One link, however, in the chain is necessarily wanting in human pathology. We are not able, when we wish to observe the particular phase of an endocarditis, to look and see.

Transitional cases of rheumatic endocarditis, by which then we imply cases hovering on the border-line of the divisions, simple or non-infective, and malignant or infective endocarditis, are of frequent occurrence.

In records we repeatedly meet with cases which are thought to be malignant and have quieted down, or have been considered simple and proved to be malignant. From time to time a post-mortem examination shows us evidence of an old malignant process in a valve by the presence of a large calcified vegetation. There is, however, no necessity for this particular evidence, for the malignancy does not depend upon the size and shape of vegetations but rather upon the virulence and number of the infective agent.

As an example in illustration may be quoted the following case: A girl of twelve had suffered from an attack of acute rheumatism three months before she came under observation. From this attack she never thoroughly recovered and a relapse of polyarthritis occurred, with a slowly progressive endocarditis of the mitral and aortic valves. When death occurred five months later from cerebral embolism, a calcareous mass of vegetation was found upon the cusp of the aortic valve, and on the thickened mitral valve there were small recent vegetations.

This group of transitional cases is purely artificial and is not likely to content any one, for it is built up partly upon clinical, partly upon experimental,

and partly upon pathological evidence, and in some cases reliance has to be placed upon one source, in others upon another source of evidence.

We have, we repeat, only used the term here in order to show how advisable it is to abandon the terms 'simple' and 'malignant' as applied to rheumatic endocarditis, and by the formation of such a group to do what little we can to break down the barrier caused by the terms 'infective' and 'non-infective' endocarditis.

The examples that we give in this group can be supplemented by others in Group I and Group III.

GROUP No. II.

Transitional Cases. Linked to Group I by Cases 3, 6, 12, *and* 18 *in that Group.*

No. 1. Female, aged 10. **History of acute rheumatism** : First attack. **Main symptoms of final illness** : Admitted for multiple arthritis and heart disease. Ran a course with moderate irregular fever. The spleen enlarged and the mitral and aortic lesions proved fatal. **Approximate duration** : 11 weeks. **Bacteriology** : None made. **Result** : *Death.* The vegetations on the mitral and aortic valves were quite small, but the condition of the spleen and course of the case were in accordance with malignant endocarditis. There was no pericarditis.

No. 2. Female, aged 12. **History of acute rheumatism** : An attack 3 months before, never well since. **Main symptoms of final illness** : For many weeks slowly losing ground with multiple arthritis. Aortic and mitral disease. Fever for the last 3 weeks continuous, and finally cerebral embolism. **Approximate duration** : 20 weeks. **Bacteriology** : Negative. **Result** : *Death.* The mitral valve was thickened and there were some recent small vegetations. The aortic showed a calcareous mass on one of the segments—suggesting a healed malignant vegetation.

No. 3. Male, aged 46. **History of chorea** at 9 years. **Main symptoms of final illness** : A long illness commencing with polyarthritis. Mitral disease was followed by the appearance of aortic disease. There was continued fever, with enlargement and tenderness of the spleen and blood and albumin in the urine. **Approximate duration** : 16 weeks. **Bacteriology** : Negative. **Result** : There was *recovery* from all the acute symptoms. It is difficult to explain the clinical course except as due to a transient malignancy.

No. 4. Female, aged 44. **History of rheumatic fever** at 25 and 34 years. **Main symptoms of final illness** : Admitted with aortic and mitral disease with continuous irregular fever; developed haemoptysis and sudden pain in the left side. **Approximate duration** : 9 weeks. **Bacteriology** : Negative. **Result** : There was a *slow recovery*. All the acute symptoms subsided.

No. 5. Male, aged 13. **History of acute rheumatism** : First attack. **Main symptoms of final illness** : Developed aortic and mitral disease with irregular fever. The clinical diagnosis was malignant endocarditis. **Approximate duration** : 10 weeks. **Bacteriology** : Negative. **Result** : *Relieved.* All acute symptoms disappeared.

No. 6. Male, aged 38. **History of acute rheumatism** : 3 attacks. **Main symptoms of final illness** : Aortic and mitral disease with persistent fever for 7 weeks and cerebral embolism. Later signs of asystole. **Approximate duration** : 12 weeks. **Bacteriology** : Negative. **Result** : *Relieved.* Eventually all acute symptoms subsided and the patient made a partial recovery.

No. 7. Male, aged 28. **History of acute rheumatism** at 24 years. **Main symptoms of final illness** : Admitted for active mitral disease; developed aortic regurgitation with persistent fever for 12 weeks. No emboli noted. **Approximate duration** : 16 weeks.

Bacteriology: Negative. **Result**: *Relieved*. Thought to be malignant, but the acute symptoms quieted down.

No. 8. Male, aged 58. **History of acute rheumatism** at 30 and 42 years. **Main symptoms of final illness**: A case of aortic and mitral disease with irregular fever for 3 months and blood and albumin in the urine. **Approximate duration**: 12 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 9. Female, aged 22. **History of acute rheumatism** as a child; repeated attacks since. **Main symptoms of final illness**: Admitted with aortic and mitral disease, irregular fever, haematuria, and ophthalmoplegia. Recovered partially, but 5 months later readmitted with nephritis. **Approximate duration**: 4 weeks. **Bacteriology**: None made. **Result**: *Death*. The necropsy showed old pericarditis. Thickened mitral and aortic valves, a large spleen. Large white kidneys with scars of previous infarctions.

No. 10. Female, aged 25. **History of acute rheumatism** at 17 years. **Main symptoms of final illness**: Admitted with slight fever; ophthalmoplegia, renal infarctions. **Approximate duration**: 7 weeks. **Bacteriology**: Negative. **Result**: *Relieved*.

No. 11. Male, aged 15–17. **History of acute rheumatism** at 12 and 13 years. **Main symptoms of first illness** (at 15): Arthritis and mitral and aortic disease, fever. **Approximate duration**: 4 weeks. **Bacteriology**: None made. **Result**: Simple acute rheumatism. **Main symptoms of second illness** (at 16): Carditis and high irregular fever for 8 weeks. **Approximate duration**: 12 weeks. **Bacteriology**: None made. **Result**: Suspected to be malignant. **Main symptoms of third illness** (at 17): Carditis with 100 days' fever, pleurisy. **Approximate duration**: 17 weeks. **Bacteriology**: Negative. **Result**: Suspected to be malignant but *recovered*.

No. 12. Female, aged 14. **History of acute rheumatism** at 11 years. **Main symptoms of final illness**: Admitted with polyarthritis, aortic and mitral disease. There were no evidences of embolism, but persistent fever for 9 weeks. **Approximate duration**: 9 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 13. Female, aged 10. **History of chorea** and rheumatism at 8 and 9 years. **Main symptoms of final illness**: Admitted with polyarthritis, aortic and mitral disease, persistent fever for 9 weeks. **Approximate duration**: 9 weeks. **Bacteriology**: None made. **Result**: *Death*. Adherent pericardium. Aortic and mitral endocarditis of the acute rheumatic type, but the spleen enlarged.

GROUP III.

Acute Rheumatic Heart Disease (Simple Type).

This group needs no explanation. The classical examples are found in the young, and the fatal first attacks are valuable illustrations of the fact that death results from a pancarditis, and not from the simple endocarditis. Here we would again repeat that in most of the opportunities for examining the vegetations of simple rheumatic endocarditis the actual process in the valves is in a stage of retrogression; it is only in rare exceptions that a condition can be obtained comparable to an early experimental endocarditis in which an animal can be killed as soon as the signs develop.

In several instances the cases with recurrent attacks of rheumatism illustrate the increasing obstinacy of the cardiac infection, with its repetition, and also show that the relation of a recurrent attack to previous ones precisely resembles that which exists between the malignant cases and a previous attack of acute rheumatism, for the time interval may be short or long.

GROUP No. III.

Acute Rheumatic Endocarditis. Linked up to Group II by Cases 11, 12, and 13 in that Group and 3, 9, and 10 in this.

No. 1.   Male, aged 4½. **History of acute rheumatism** : First attack. **Main symptoms of final illness** : Polyarthritis, subsiding. Aortic and mitral disease, pericarditis and nodules, persistent fever. **Approximate duration** : 12 weeks. **Bacteriology** : None made. **Result** : *Death.* Subacute pericarditis, acute simple aortic and mitral endocarditis.

No. 2.   Male, aged 9. **History of acute rheumatism** : First attack. **Main symptoms of final illness** : 5 weeks' fever with arthritis, nodules, and aortic and mitral disease. **Approximate duration** : 5 weeks. **Bacteriology** : None made. **Result** : *Death.* Acute simple aortic and mitral endocarditis.

No. 3.   Female, aged 9¼. **History of acute rheumatism** : First attack. **Main symptoms of final illness** : Arthritis, carditis and chorea, persistent irregular fever. **Approximate duration** : 5 weeks. **Bacteriology** : Strepto-diplococcus isolated. **Result** : *Death.* Acute simple endocarditis, though aortic vegetations larger, resembling those of a malignant case. Recent pericarditis.

No. 4.   Male, aged 9. **History of acute rheumatism** at 8 years (6 months ill). **Main symptoms of final illness** : Acute endocarditis and nodules ; 9 weeks' fever. **Approximate duration** : 10 weeks. **Bacteriology** : None made. **Result** : *Death.* Adherent pericardium. Mitral and aortic endocarditis, recent vegetations, thickened valves.

No. 5.   Male, aged 10–11⅓. **History of acute rheumatism** : First attack at 10 years ; second attack at 11½ years. **Main symptoms of first illness** : Arthritis, persistent fever for many weeks, of the typhoidal type ; aortic and mitral disease. **Approximate duration** : 20 weeks. **Bacteriology** : None made. **Main symptoms of second illness** : Asystole. **Approximate duration** : 2 weeks. **Bacteriology** : None made. **Result** : *Death.* Thickened aortic valves, with minute vegetations, aortic atheroma.

No. 6.   Female, aged 7. **History of acute rheumatism** at 6 years. **Main symptoms of final illness** : Arthritis. Continuous irregular fever, aortic and mitral disease. **Approximate duration** : 12 weeks. **Bacteriology** : None made. **Result** : *Death.* Slight recent aortic endocarditis. Old and recent mitral.

No. 7.   Female, aged 6¼. **History of acute rheumatism** at 4 and 5 years with pericarditis. **Main symptoms of final illness** : Asystole, with slight fever. **Approximate duration** : 5 weeks. **Bacteriology** : None made. **Result** : *Death.* Mitral aortic and tricuspid endocarditis of the acute rheumatic type. No evidence of pericarditis.

No. 8.   Female, aged 16. **History of acute rheumatism** : First attack. **Main symptoms of final illness** : Commenced with polyarthritis, 10 weeks' fever, gradually subsiding. Aortic and mitral disease. **Approximate duration** : 13 weeks. **Bacteriology** : None made. **Result** : *Relieved.*

No. 9.   Female, aged 6–8. **History of acute rheumatism** : First attack at 6 years ; second attack at 7 years ; third attack at 8 years. **Main symptoms of first illness** : Arthritis, chorea, nodules, persistent carditis, aortic and mitral disease, waves of fever extending over many weeks. **Approximate duration** : At least 18 weeks. **Bacteriology** : None made. **Result** : *Relieved.* **Main symptoms of second illness** : Carditis, persistent fever.   **Approximate duration** : 12 weeks. **Bacteriology** : None made. **Result** : *Relieved.* **Main symptoms of third illness** : 10 days' fever, asystole. **Approximate duration** : 10 days. **Bacteriology** : Strepto-diplococcus isolated from mitral valve. **Result** : *Death.* Recent and old pericarditis, aortic valves inflamed from base to margin.

No. 10.   Male, aged 11–16½. **History of chorea** at 3 years ; acute rheumatism at 11, 12, 14, 16, and 16½ years. **Main symptoms of first illness** : Aortic and mitral disease, nodules, persistent fever. **Approximate duration** : 20 weeks. **Bacteriology** : None made. **Result** : Simple mitral endocarditis. **Main symptoms of second illness** : Sent in for 'a rest', persistent fever and tachycardia for 3 weeks. **Approximate duration** : 3 weeks. **Bacteriology** : None made. **Result** : *Relieved.* **Main symptoms of third illness** : Three weeks' palpitation and fever. **Approximate duration** : 5 weeks. **Bacteriology** : None made.

Result: *Relieved*. **Main symptoms of fourth illness**: 10 weeks' pericarditis and carditis. **Approximate duration**: 12 weeks. **Bacteriology**: Blood culture negative. **Result**: *Relieved*. **Fifth illness—Result**: *Sudden death*. No post-mortem; probably the simple type. Note persistent carditis with fever.

No. 11. Female, aged 17. **History of acute rheumatism** at 10 years and 2 attacks since. **Main symptoms of final illness**: Admitted with mitral regurgitations and slight fever; developed aortic regurgitations and died suddenly. **Approximate duration**: 3 weeks. **Bacteriology**: None made. **Result**: *Death*. No post-mortem.

No. 12. Male, aged 22. **History of acute rheumatism** at 11 and 17 years. **Main symptoms of final illness**: Multiple arthritis. Aortic and mitral disease with irregular outbursts of fever, synchronous with which there was precordial pain. **Approximate duration**: 8 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 13. Male, aged 22. **History of acute rheumatism** at 18 and 20 years. **Main symptoms of final illness**: 5 months' history of recurrent anginal attacks, also multiple arthritis, aortic and mitral disease and recurrent attacks of fever. **Approximate duration**: 8 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 14. Male, aged 50. **History of acute rheumatism** in childhood and at 25 years. **Main symptoms of final illness**: Aortic and mitral disease, with irregular fever for 7 days. **Approximate duration**: 6 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 15. Female, aged 10. **History of acute rheumatism** at 7 and 8 years. **Main symptoms of final illness**: Polyarthritis, aortic and mitral, tachycardia, high irregular fever followed by a normal temperature and relapse. **Approximate duration**: 5 weeks. **Bacteriology**: None made. **Result**: *Relieved*. Severe type of simple carditis.

No. 16. Male, aged 38. **History of acute rheumatism** at 6, 12, and 21 years. **Main symptoms of final illness**: Mitral and aortic disease with 3 attacks of fever, in one of which an attack of pericarditis. **Approximate duration**: 10 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 17. Female, aged 20. **History of acute rheumatism** at 6 and 12 years; chorea at 15 years. **Main symptoms of final illness**: Double mitral and aortic regurgitation with slight transient fever. **Approximate duration**: 4 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 18. Male, aged 25. **History of acute rheumatism**: Several mild attacks. **Main symptoms of final illness**: Polyarthritis, transient fever, mitral and aortic disease. **Approximate duration**: 7 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 19. Male, aged 32. **History of acute rheumatism** at 11, 16, and 26 years. **Main symptoms of final illness**: Mitral and aortic disease, left with a rising temperature. **Approximate duration**: 13 weeks. **Bacteriology**: None made. **Result**: Left at own request, nature of endocarditis doubtful.

No. 20. Female, aged 18. **History of acute rheumatism**: 6 attacks. **Main symptoms of final illness**: Mitral and aortic disease, 3 weeks' irregular fever, pericarditis, several relapses of fever. **Approximate duration**: 13 weeks. **Bacteriology**: None made. **Result**: *Relieved*. Severe type.

No. 21. Female, aged 24. **History of chorea** at 9 years; acute rheumatism at 16 years. **Main symptoms of final illness**: Mitral and aortic disease with slight fever. **Approximate duration**: 5 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 22. Female, aged 20. **History of acute rheumatism**: First attack. **Main symptoms of final illness**: Multiple arthritis, aortic and mitral regurgitations, always a slightly swinging temperature. **Approximate duration**: 11 weeks. **Bacteriology**: Blood culture negative. **Result**: *Relieved*. Note persistent slight fever.

No. 23. Male, aged 13. **History of acute rheumatism** at $11\frac{1}{2}$ years. **Main symptoms of final illness**: Aortic and mitral disease, arthritis, nodules, slight fever. **Approximate duration**: 7 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 24. Male, aged 27. **History of acute rheumatism** at 21 years. **Main symptoms of final illness**: Dyspnoea, mitral and aortic disease, slight irregular fever. **Approximate duration**: 5 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 25. Male, aged 21. **History of acute rheumatism** at 10 and 11 years. **Main**

symptoms of final illness: Subacute arthritis, mitral and aortic disease, slight fever. Approximate duration: 3 weeks. Bacteriology: None made. Result: *Relieved*.

No. 26. Male, aged 24. **History of acute rheumatism** at 11 years. **Main symptoms of final illness**: Arthritis, mitral and aortic disease, and irregular fever. **Approximate duration**: 7 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 27. Male, aged 22. **History of acute rheumatism**: First attack. **Main symptoms of final illness**: Arthritis followed by mitral and then aortic regurgitations, always a slight fever, never rising above 100° F. **Approximate duration**: 17 weeks. **Bacteriology**: None made. **Result**: *Relieved*. Note the mild but progressive course.

No. 28. Female, aged 35. **History of acute rheumatism** at 14 years. **Main symptoms of final illness**: Arthritis, mitral and aortic disease and slight fever. **Approximate duration**: 5 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 29. Female, aged 11. **History of acute rheumatism** at 8 and 9 years. **Main symptoms of final illness**: Mitral and aortic disease; only in hospital 10 days. **Approximate duration**: 10 days. **Bacteriology**: None made. **Result**: *Relieved*.

No. 30. Female, aged 34. **History of acute rheumatism**: 6 attacks. **Main symptoms of final illness**: Mitral and aortic disease. **Approximate duration**: 5 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

No. 31. Male, aged 10. **History of acute rheumatism** at 6 years. **Main symptoms of final illness**: Pericarditis, aortic and mitral disease, nodules and arthritis, fever for 14 days ill 12 weeks. **Approximate duration**: 12 weeks. **Bacteriology**: None made. **Result**: *Death*. Thickened aortic and mitral with recent vegetations (small). Recent pericarditis.

No. 32. Female, aged 19. **History of rheumatism** and chorea at 13 years. **Main symptoms of final illness**: Severe aortic and mitral disease with continuous fever for 5 weeks; anginal attacks. **Approximate duration**: 5 weeks. **Bacteriology**: None made. **Result**: *Relieved*. Note prolonged fever, carditis, and angina.

No. 33. Female, aged 38. **History of acute rheumatism** at 14 years. **Main symptoms of final illness**: Mitral and aortic disease, admitted with transient polyarthritis and fever. **Approximate duration**: 5 weeks. **Bacteriology**: None made. **Result**: *Relieved*.

CASES IN GROUP IV.

The last group of cases will not need any prolonged explanation, for they are examples of heart scars with consequent mechanical disabilities. There is a sufficient number of fatal cases among them in which a necropsy has proved the reality of such an interpretation, and their chief importance is to emphasize the power that the human frame possesses to resist the rheumatic infection. This very fact bringing it strictly into line with other great infections only serves to throw into relief the overwhelming probability that these healing processes may also fail, as they do undoubtedly succeed, in such a struggle. What an assumption it must be to assert that such an infection as the rheumatic could always be overcome in the cardiac valves! Even if we were deprived of all the clinical, pathological, and experimental evidence we now possess such an assumption would be open to the gravest questioning, but with such evidence at hand it must surely be abandoned as a survival of an older pathology which existed when acute rheumatism was looked upon as of nervous or lactic acid origin. Old beliefs die very hard, and oftentimes in medical literature may be seen the strange results of attempting to graft upon an old stem the new shoots of another plant of knowledge. The relationship of rheumatism to malignant endocarditis is a beautiful example of such an attempt. Every sort of ingenious device has been invented to graft the old stem with the new shoots, but they have all failed.

Among the most remarkable must be placed that one which suggests that rheumatism is a mysterious and unknown disease akin to simple scarlet fever, upon which all the manifestations are to be grafted as secondary infections. When we can imagine on the one hand a scarlet fever which is not infectious and is without a rash save in exceptional cases, and on the other a rheumatism which is infectious and which possesses no manifestations except possibly a sore throat and an occasional rash, we may be able to appreciate the likeness between these two diseases. For us an infectious disease such as scarlet fever, whether complicated by secondary infections or not, possesses a peculiarity of its own, viz. its infectivity. Whereas acute rheumatism, deprived of its manifestations, is a disease still to be discovered, as also would be in our opinion a tuberculosis or pneumococcal infection without its manifestations.

GROUP No. IV.

Chronic Heart Disease due to previous Rheumatic Endocarditis.

A. Cases showing chiefly aortic symptoms.

No. 1. Male, aged 63. **History of acute rheumatism:** 3 attacks; heart disease at 13 years. **Main symptoms of final illness:** 2 days' illness. Sudden death, aortic type, mitral and aortic disease. **Approximate duration:** 2 days. **Result:** *Death.* Calcified valves.

No. 2. Male, aged 42. **History of much rheumatism. Main symptoms of final illness:** Angina pectoris—dyspnoea, aortic and mitral disease. **Approximate duration:** Many weeks. **Result:** *Death.* Thickened valves and aortic atheroma.

No. 3. Male, aged 40. **History of acute rheumatism at 27. Main symptoms of final illness:** Mitral and aortic disease, angina pectoris. **Approximate duration:** 4 weeks. **Result:** *Relieved.*

No. 4. Male, aged 40. **History of acute rheumatism:** Repeated attacks. **Main symptoms of final illness:** Mitral and aortic disease with angina. **Approximate duration:** 6 weeks. **Result:** *Relieved.*

No. 5. Female, aged 14. **History of acute rheumatism:** Slight. **Main symptoms of final illness:** Mitral and aortic disease, pallor, pain in chest. **Approximate duration:** 9 days. **Result:** *Relieved.*

No. 6. Male, aged 28. **History of acute rheumatism** at 18 years and since. **Main symptoms of final illness:** Mitral and aortic disease, dyspnoea. **Approximate duration:** 7 days. **Result:** Left at his own request.

No. 7. Male, aged 48. **History of acute rheumatism** at 35 and 39 years. **Main symptoms of final illness:** Mitral and aortic disease, angina. **Approximate duration:** 3 weeks. **Result:** *Relieved.*

B. Cases showing chiefly mitral symptoms.

No. 1. Male, aged 38. **History of acute rheumatism:** Several attacks. **Main symptoms of final illness:** Alcoholism. Mitral and aortic disease, jaundice, dropsy, dyspnoea. **Approximate duration:** 11 weeks. **Result:** *Death.* Sclerosis of aortic and mitral valves.

No. 2. Male, aged 50. **History of acute rheumatism** at 8, 25, 36, and 49 years. **Main symptoms of final illness:** Mitral and aortic. Oedema, dyspnoea, &c.; asystole. **Approximate duration:** Many weeks. **Result:** *Death.* Calcified aortic and mitral valves; shortening of chordae tendineae.

No. 3. Male, aged 72. **History of acute rheumatism** at 17 years. **Main symptoms of**

final illness : Mitral and aortic. Myocardial weakness. Asystole. **Approximate duration** : 4 weeks. **Result** : *Death*. Thickened mitral and aortic valves. Atheroma.

No. 4. Female, aged 52. **History of acute rheumatism at 40 years. Main symptoms** of final illness: Mitral and aortic. Asystole, with oedema, &c. **Approximate duration** : 4 weeks. **Result** : *Relieved*.

No. 5. Female, aged 60. **History of acute rheumatism** : Slight attacks. **Main** symptoms of final illness : Mitral and aortic. Asystole, with cyanosis and dropsy. **Approximate duration** : 5 weeks. **Result** : *Relieved*.

No. 6. Female, aged 79. **History of acute rheumatism** : 6 attacks. **Main symptoms** of final illness : Mitral and aortic. Asystole—mitral type. **Approximate duration** : 5 weeks. **Result** : *Relieved*.

No. 7. Male, aged 35. **History of acute rheumatism at 20 years. Main symptoms** of final illness : Mitral and aortic. Alcoholism, asystole. **Approximate duration** : 5 weeks. **Result** : *Relieved*.

No. 8. Male, aged 20. **History of acute rheumatism** at 11 years. **Main symptoms** of final illness: Mitral and aortic. Asystole—mitral type. **Approximate duration** : 3 weeks. **Result** : *Relieved*.

No. 9. Female, aged 18. **History of acute rheumatism at 13, 14 and 15 years. Main** symptoms of final illness : Mitral and aortic. Murmurs. **Approximate duration** : 2 weeks. **Result** : *Relieved*.

No. 10. Female, aged 26. **History of acute rheumatism** : Repeated attacks. **Main** symptoms of final illness : Mitral and aortic. Severe asystole, mitral type. **Approximate duration** : 24 weeks. **Result** : *Relieved*.

No. 11. Female, aged 20. **History of acute rheumatism** : 6 attacks. **Main symptoms** of final illness : Mitral and aortic disease. Signs of mitral asystole. **Approximate duration** : 4 weeks. **Result** : *Relieved*.

No. 12. Male, aged 40. **History of acute rheumatism at 19 years. Main symptoms** of final illness : Mitral and aortic disease. Signs of mitral asystole. **Approximate duration** : 10 weeks. **Result** : *Relieved*.

No. 13. Male, aged 48. **History of acute rheumatism at 12 and 38 years. Main** symptoms of final illness : Mitral and aortic disease. Signs of asystole. **Approximate duration** : Some weeks. **Result** : *Relieved*.

No. 14. Male, aged 22. **History of acute rheumatism at 19 years. Main symptoms** of final illness : Mitral and aortic disease. Signs of asystole, mitral. **Approximate duration** : 3 weeks. **Result** : *Relieved*.

No. 15. Male, aged 22. **History of acute rheumatism at 16 years. Main symptoms** of final illness : Mitral and aortic disease, prolonged asystole. **Approximate duration** : 18 months. **Result** : *Relieved*.

No. 16. Female, aged 32. **History of acute rheumatism at 14, 19, 21, 23, and 25 years.** **Main symptoms of final illness** : Mitral and aortic disease, with palpitation. **Approximate duration** : 7 days. **Result** : *Relieved*.

No. 17. Female, aged 32. **History of acute rheumatism at 17 and 31 years. Main** symptoms of final illness : Mitral and aortic disease, with signs of mitral asystole. **Approximate duration** : 4 weeks. **Result** : *Relieved*.

No. 18. Female, aged 33. **History of acute rheumatism** as a child. **Main symptoms** of final illness : Mitral and aortic disease. Palpitation, &c. **Approximate duration** : 10 days. **Result** : *Relieved*.

No. 19. Female, aged 21. **History of acute rheumatism at 11 and 12 years. Main** symptoms of final illness : Mitral and aortic disease. Anaemia, palpitation, &c. **Approximate duration** : Many months. **Result** : *Relieved*.

No. 20. Female, aged 28. **History of acute rheumatism** as a child and at 18 years. **Main symptoms of final illness** : Mitral and aortic disease. Asystole. **Approximate duration** : Many weeks. **Result** : *Relieved*.

No. 21. Male, aged 14. **History of acute rheumatism** at 12 years. **Main symptoms** of final illness : Mitral and aortic disease. Severe asystole. **Approximate duration** : 4 weeks. **Result** : *Death*. Aortic and mitral valves thickened, adherent pericardium.

No. 22.   Male, aged 30.   **History of acute rheumatism** at 16 years.   **Main symptoms of final illness**: Mitral and aortic disease.   Signs of asystole.   **Approximate duration**: 3 weeks.   **Result**: *Relieved.*

We wish now to put very briefly our conception of acute rheumatism—or, as we would prefer to call it, rheumatism—side by side with the pictures of other similar infections.

1. First of all comes the gonorrhoeal infection.

From a local focus in the urethra there may follow a systemic invasion, producing multiple arthritis and other lesions, including a carditis.   The arthritis may be transient, but often is exceedingly stubborn and drifts into a condition of rheumatoid arthritis.   The heart affection may be a pancarditis, or a transient endocarditis, or a malignant endocarditis.

2. The rheumatic infection from such a focus as the tonsil may produce an arthritis and other lesions, including a carditis.   Two features are well recognized. One is that the arthritis is usually transient, although we maintain that a rheumatoid arthritis may result from this infection.   The other is the great prominence of cardiac lesions.   Carditis is very frequent, and both simple and malignant endocarditis may result.

3. With the pneumococcal infection the lungs and pleurae take the position that the heart occupies in rheumatism, but arthritis of all grades of severity may result, and also a carditis, in which suppurative pericarditis and malignant endocarditis are liable to develop.

4. In staphylococcal infections, from a local infection such as an acute osteomyelitis, there may follow multiple arthritis and carditis.   The processes here are essentially suppurative, and multiple nodular subcutaneous abscesses, myocardial abscesses, and acute malignant endocarditis may all result.

5. Virulent streptococcal infections of the type caused by the *Streptococcus pyogenes* show a similar picture.   The arthritis, if not exceedingly acute, is suppurative; profound myocardial poisoning is much more frequent than endocarditis, and this, when it occurs, is usually malignant in type.   A general septicaemia is frequent, and in classical cases the entire process differs widely from that of acute rheumatism.   It is a difference in the type and not in the degree of virulence.

We believe that this conception of acute rheumatism as a peculiar streptococcal infection fills a gap in our knowledge of this important disease, in a way that is unequalled, not only for its simplicity, but for the completeness of the explanation which it affords of the symptoms and course of the affection.

The strong hereditary element in the disease supports the view that the exciting cause possesses some peculiarity by which in these particular tissues it can form the special poisons that make it so definite an affection.

Concluding Remarks.

We believe that the view we support in this research is not one of academic interest or a mere battle of words. It will be a distinct gain if we succeed in overthrowing the remarkable view that the nature of rheumatic endocarditis—whatever the infection may be—is always benign and requires an added infection to produce a progressive lesion. The survival of such a view implies such a subversion of the natural principles of the infective processes as to unsteady one's whole outlook upon these diseases. The disappearance of such a mystery, on the other hand, must be a clear gain to connected thought upon all rheumatic processes and a forward step in cardiac pathology.

Far more important is its bearing upon the clinical side of malignant endocarditis. The rheumatic form is no exception to the rule that it is a disease which is almost invariably fatal when the signs are well established. Theoretical considerations lead to the belief that occasional recoveries may occur, and there is good clinical evidence in support; but these exceptions are rare, and our series alone shows the great fatality.

We are doubtful of the efficacy of serum or vaccine at present in use, though we would neither dispute the records of such recoveries while such treatment was being employed, nor the advisability of trying any method that holds out the least prospect of success.

It is the prophylaxis that is encouraged by our investigations. There must clearly be some peculiar factors at work to produce the progressive endocarditis, and we sometimes find suggestive evidence in support of this. The cardiac rheumatism may have been neglected, the patient ill-fed, the surroundings unhealthy. Anaemia—a prominent feature of some rheumatic attacks—may have persisted, and this in our opinion favours the malignant process. The danger of large unhealthy tonsils in the rheumatic is well established, and this danger can be cautiously dealt with. Above all, we believe that more clinical study is necessary of the course and history of acute rheumatic endocarditis. We believe that a smouldering activity of the rheumatic process is more common than is suspected, and very possibly we may not yet possess the necessary clinical accuracy for ascertaining the limits of this activity. This seems the more likely when we bear in mind that even a gross and progressive lesion may elude our observation until the end is close at hand.

There is more hope that we may protect a patient against the development of a known danger than against a mysterious secondary infection which prefers scarred valve tissues and which appears usually without any particular cause or reason.

The disappearance of the terms 'malignant', 'infective', or 'pernicious' as applied to endocarditis will be a great advantage, and the substitution of the term 'active' will answer every purpose, for the physician can judge of the degree

of this activity by the well-known signs that may arise. 'Active tuberculosis' expresses sufficiently a progressive pulmonary lesion, and we need no term 'malignant tuberculosis' to bring home to us the fact that the activity is getting beyond all control. Why then use such a term as 'malignant endocarditis', or perpetuate such an unproven conception as a non-infective endocarditis, by the use of the adjective 'infective'?

DESCRIPTION OF FIGURES.

PLATE 27.   To illustrate the view that direct spread of infection may occur from one valve to another.

FIG. 1.   The heart of a rabbit showing endocarditis of the mitral and aortic valves.   The heart has been greatly enlarged for the more convenient comparison with the human heart. The vegetations on the mitral valve are very extensive and are in continuity with equally extensive ones upon the aortic cusps.

FIG. 1 a.   A human heart showing aortic and mitral endocarditis.   The vegetations on the aortic flap of the mitral are in continuity with extensive vegetations on the contingent aortic cusp.   The other cusps are affected in lesser degree.   The mitral valve is not opened.

PLATE 28, FIG. 2.   The heart of a rabbit showing mitral endocarditis of the malignant type, the result of infection with the *Diplococcus rheumaticus*.

FIG. 3.   The heart of a rabbit showing fibrino-plastic pericarditis, the result of infection with the *Diplococcus rheumaticus*.

FIG. 4.   The heart of a rabbit showing aortic endocarditis of the same causation.

FIG. 5.   Rheumatic endocarditis, human (simple type), showing the presence of the diplococci.

FIG. 6.   Rheumatic endocarditis, experimental (simple type), showing the presence of the diplococci.

FIG. 7.   Rheumatic endocarditis, human (simple type), showing the necrotic tissue in a vegetation.

PLATE 29, FIG. 8.   Rheumatic endocarditis, experimental (simple type), showing the necrotic tissue in a vegetation.

FIG. 9.   Rheumatic endocarditis, human (malignant type), showing numerous diplococci in necrotic tissue.

FIG. 10.   The same experimentally produced in a rabbit.

FIG. 11.   Early rheumatic endocarditis (human) showing numerous diplococci.

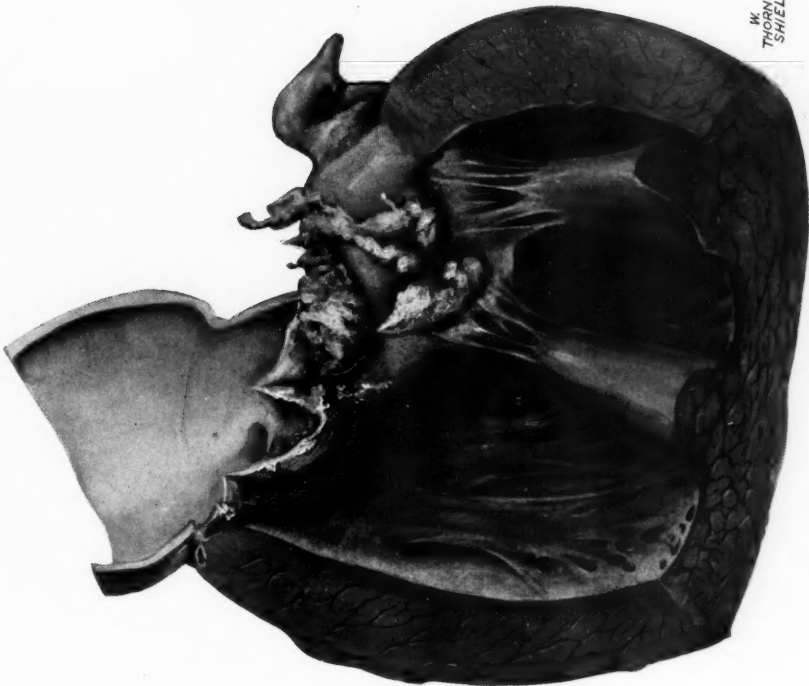FIG. 12.   Transitional type of endocarditis in a rabbit.

W.
THORNTON
SHIELLS.

FIG. Ia

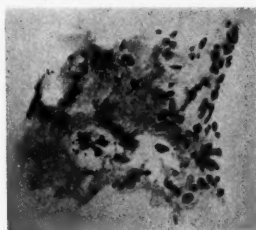
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THORNTON
SHIELLS.

FIG. I

Fig. 2

Fig. 4

Fig. 3

Fig. 5

Fig. 6

Necrotic tissue

Attachment of vegetation
to valve.
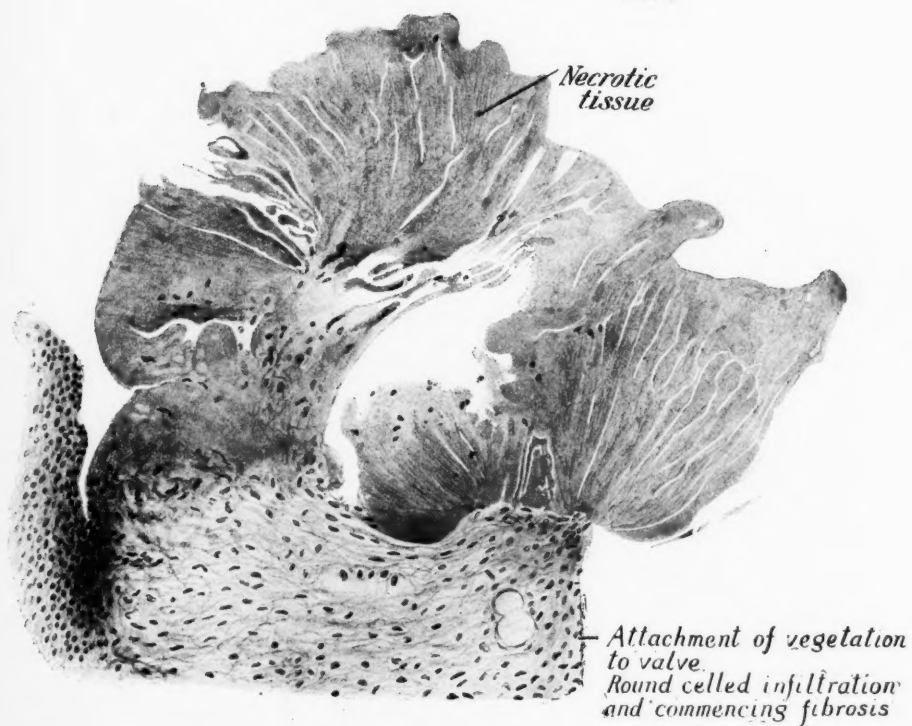Round celled infiltration
and commencing fibrosis
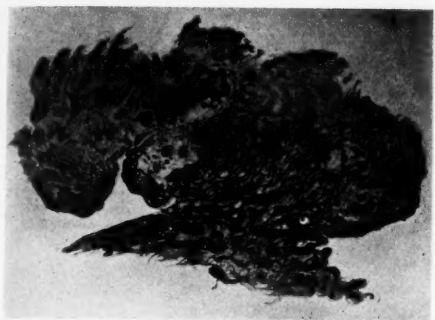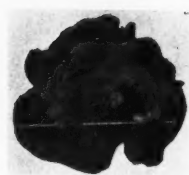
Fig. 7

Fig. 8

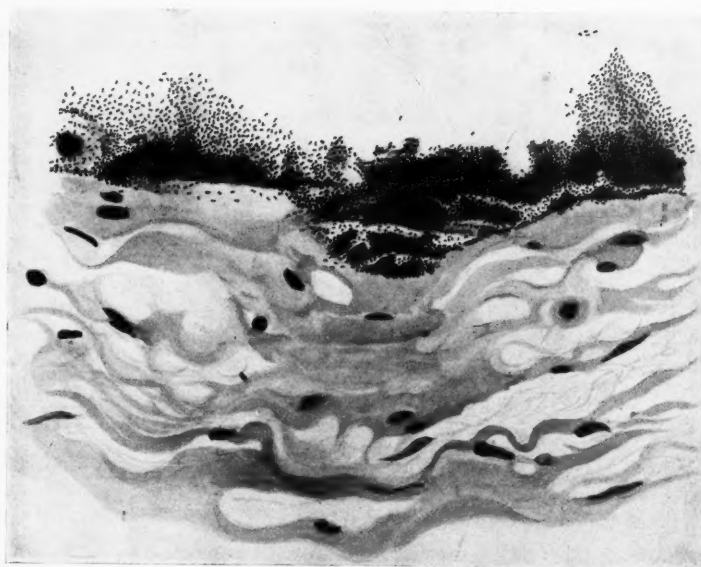Fig. 9

Fig. 10

Fig. 12

Fig. 11

A CASE OF THOMSEN'S DISEASE

By LEONARD FINDLAY

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With Plates 30–34

J. McD., aged 28 years, unmarried and a car-conductor by occupation, was first seen by me at the Western Infirmary Dispensary on January 10, 1912. He complained of a stiffness of his legs and arms whenever he started to move them after resting.

History of present illness. The patient dates this illness from the age of 6 years, at which time he went to school and had to ascend stairs to reach his class-room. Then he first noticed that his legs got stiff on commencing to go upstairs, and that he lagged behind the rest of the boys, but very shortly after taking a few steps the rigidity would relax, and he could run up the remaining steps as quickly as any of his class-mates. The same unyielding character of his legs was manifested on rising from a chair and suddenly attempting to walk, e. g. on getting up from the table after a meal. The first few steps he would make very slowly, but very soon the disability would pass off. He had also experienced some want of pliancy in the arms on suddenly bringing them into action, and of the fingers on first attempting to open the hand after having firmly closed it. This affection of his arms was the cause of much inconvenience when he was having a round at boxing, as he always had to take a few blows before his arms got sufficiently supple to enable him to ward off his opponent. The same stiff sensation he had felt in the eyelids and also in the muscles of the jaw, but never on swallowing, micturating, or defaecating. This stiffness was never associated with pain, nor had it caused him serious inconvenience, since he had been able to enjoy games like other boys, and had never had an accident which he can ascribe to it. In view of his employment particular inquiry was made regarding this latter point, but he was quite decided that he had never had a mishap due to this want of control over his limbs, though he admitted that he does not know what might happen if he had to perform some movement very quickly, as e. g. jumping off a car in motion. His one complaint was that the condition made him look foolish, as on going upstairs he at first lagged behind, and his companions turned round to see what was wrong. There was no factor, which, so far as he knew, influenced the condition ; it was as bad in cold weather as in hot, and it was not made worse by heat or excitement. He said that he was not of an emotional nature, but he stated that he was rather subject to blushing. His incapacity was always the same ; it occurred during the first few movements after a period of rest, be this period long or short, and passed off very quickly. Otherwise he had always enjoyed good health.

Family history. There was no record of a similar condition or of other nervous disease in his own family or relatives. His father, who in his time was a great 'Highland dancer', died at the age of 68 from an accident. His mother, aged 68, one brother, and one sister were all alive and well.

Present condition. The patient appeared healthy, was well built and looked unusually muscular, but if anything his power was deficient ; certainly he was not stronger than the average. With the dynamometer the grasp of his right hand

registered 180–190, and of his left hand 160–180, while the corresponding figures for myself were 200 and 180.   The muscles were not unduly firm.   Excepting for the peculiarity in his actions nothing abnormal was detected.   If the patient was asked to perform some movement, such as flexing the arm at the elbow, it was seen that he was unable to straighten the arm for some little time, perhaps as long as 5 or 6 seconds.   On repeating the movement the same difficulty was experienced, but on this occasion the stiffness did not last so long, perhaps only a matter of 3 seconds, and when he had performed the same movement four or five times he could straighten out the arm at once, and absolutely nothing abnormal was observed.   The same condition was detected in the flexor muscles of the fingers.   After forcibly closing the hand he had difficulty in at once completely extending the fingers—the contraction of the flexors might persist for as long as 6 seconds.   The second time the relaxation occurred after a period of 3 seconds, and after the third contraction relaxation took place immediately. The muscles of the shoulder girdle, the latissimus dorsi, and also the interossei, as recently pointed out by Griffith (6), were similarly affected.

The myotonia was specially well brought out on his attempting to mount a flight of stairs.   He might make the first step all right, but, on trying to flex the other leg to accomplish the next move, he finds that he cannot do so.   He might spring off his foot to give himself the necessary impetus for the ascent, but his toes catch on the step, and he has to fall back to his old position until the spasm passes off, when he will mount the next step all right.   But the same thing occurs with the other leg, and so on for the first two or three steps with each foot, after which the limbs seem to become quite supple, and he runs up the remaining portion of the stair as quickly as anybody.   Sometimes he may have mounted a few steps before the spasm occurs, but as a rule it took place during the first few movements of ascent.   If he had been walking for some time before, he might not experience this difficulty in bending his legs on climbing a stair.

This peculiar contraction of the quadriceps was very well seen while he lay on a couch and forcibly contracted the muscle.   The first contraction after a period of rest persists for at least 6 seconds before relaxation commences, the second contraction endures for only 4 seconds, the third for 2 seconds, the fourth for only 1 second, and then the successive contractions pass off immediately. This phenomenon could be felt as well as seen.   The same condition was appreciated in the levator palpebrae superioris of both eyelids.   When asked to look upwards without moving his head, and then suddenly to turn his gaze downwards, it was noticed that the upper eyelid did not follow the eyeball, but lagged behind and left a portion of the sclerotic coat uncovered.   In a little while the eyelid takes up the normal position, and on repeating the movement once or twice all trace of the myotonia disappears.   The patient says that he felt some stiffness of the muscles of the jaw on bringing them into action, but I could not detect this myself: with the exception of the latissimus dorsi none of the muscles of the back seemed to be affected.   This muscle on voluntary movement was typically affected, whereas during coughing, as first pointed out by Beever, relaxation occurred at once.   The muscles of the abdomen, as also those employed during deglutition, defaecation, and micturition, were quite normal.

Some myographic tracings of the biceps were taken, and these show the delayed relaxation very well (tracing, Fig. 1).   It will be observed that not only is relaxation delayed, but that the second contraction occurs before complete relaxation has taken place, and that it is some time (in the tracings 10 seconds) before the muscles relax completely and the muscular contractions become normal.   After the condition passes off, however, the patient is able to make the movements with great rapidity, as a matter of fact more quickly than I can myself, as will be seen by comparing the tracings taken from my own biceps muscle (tracing, Fig. 2).   In my own case the contractions occur at the rate of one per second, while in that of the patient, after the spasm has passed off, the contractions take place at the rate of two to three per second.

With direct stimulation the muscles did not respond to a less stimulus than normally. With a slight stimulus only a few fibres contracted, but they relaxed slowly. With a stronger stimulation, e. g. hitting the muscle forcibly with a percussion hammer, the whole muscle became tonically contracted, and relaxation was delayed and unduly slow. This is well seen on eliciting the wrist-jerk by striking the muscles of the forearm (tracing, Fig. 3). Not only was relaxation slow but contraction tended to be more gradual. This peculiarity of the muscle on direct stimulation did not, as on voluntary contraction, pass off after the first few movements, but persisted as long as the contractions were induced. In the tracings of the wrist-jerk, obtained by tapping the extensors of forearm, the contractions gradually become of shorter duration, but even after thirty contractions they do not approach the normal in type. This feature of delayed relaxation was not observed on eliciting the tendon reflexes. The knee-jerks were normal in character, the contraction of the quadriceps femoris so induced being sudden in onset, and as abrupt in its relaxation. This is well shown in the tracing, Fig. 5, where the patient's knee-jerk is recorded immediately below my own. In the tracing, Fig. 6, the different behaviour of the quadriceps femoris on direct stimulation (D. S.) and while eliciting the knee-jerk (K. J.) is well seen.

Direct stimulation of the ulnar nerve by pressure with the finger did not cause contraction of the flexors of the forearm.

Electrical reactions. On stimulating the nerve (ulnar) with the Faradaic current no quantitative variation from the normal was detected. With a weak current and momentary stimulation a quick response was obtained, but with a stronger current and prolonged stimulation the relaxation was slow. With the galvanic current the same occurrence, slow relaxation after prolonged stimulation, was observed. Otherwise the reactions were normal. A. O. C. is obtained with 8 mill. amp., but even with 24 mill. amp. no K. O. C. could be perceived. On stimulating the muscles with the galvanic current no quantitative changes were remarked. On comparison with two normal individuals, the patient's muscles were found to be more sensitive than in one of the controls, but less sensitive than those of the other control individual. In the case of the biceps muscle the relaxation was distinctly slower than normal, but, as previously mentioned, this depended more on the duration of the stimulation than on the strength of the current (tracings, Figs. 7 and 8). Any current of more than 4 mill. amp., if applied long enough, induced in the patient myotonia. With a current of 18 mill. amp. a very short and sharp A. C. C. was obtained, but absolutely no K. O. C. In the case of the quadriceps femoris much stronger currents were necessary to bring about contractions, but when they did occur the same features were observed. With the Faradaic current both biceps and quadriceps muscles reacted as with the galvanic current. The same strength of current applied momentarily induced a sudden contraction which relaxed at once, but, if applied for some time, caused tonus which passed off gradually (tracing, Fig. 9).

Some experiments were conducted with my own and the patient's muscles in order to study the latent period, which has been said to be delayed in Thomsen's disease. Like Hale White (18), I did not find any variation from the normal, the latent period in both cases varying between $\frac{1}{100}$ and $\frac{1}{50}$ second. In these experiments it was found that the patient's muscles were less sensitive than my own, that the contraction was more gradual, but that it reached its maximum sooner, and that it disappeared more quickly, the duration of the contraction being $\frac{23}{100}$ second, whereas in my own case the contraction lasted $\frac{43}{100}$ second. This exemplifies the point previously mentioned—that, with momentary stimulation the muscular contraction is sudden in onset, of short duration, and does not show any delay in relaxation (tracing, Fig. 10).

The plantar reflexes were sluggish but normal, as also were the cremasteric and abdominal reflexes. The knee-jerks and tendo-Achilles jerks were normal.

Sensation was normal.

The pupils were equal and reacted normally.

Nothing unusual was detected on examination of the thorax or abdomen. Pulse and polygraph tracings showed nothing calling for remark.

The Wassermann reaction was negative.

Urine. Amber colour with a slight deposit of mucus: acid in reaction: sp. gr. 1·028. A trace of albumin was present, but neither blood nor sugar. No casts were found on minute examination of the sediment.

Dr. Macadam investigated the condition of the kreatin and kreatinin metabolism with the following results: The patient was put on a kreatin-free diet and his urine was collected for the twenty-four hours on the 4th, 5th, 6th, and on the 15th, 16th, and 17th days, when he gave up the special diet and resumed ordinary food. During this period he did not notice any change in his condition.

Date.	Output of Urine in c.c.	Total N, grms.	Kreatinin, grms.	Kreatin, grms.	Kreatinin coefficient.
Feb. 13–15	Kreatin-free diet.				
,, 16	1460	16·065	2·306	·263	14
,, 17	1675	12·756	1·993	—	12
,, 18	1725	14·49	2·242	—	13
,, 19–26	Still on kreatin-free diet.				
,, 27	1410	11·922	1·811	—	11
,, 28	1525	13·834	1·935	—	12
,, 29	1400	12·504	1·799	—	11

The points to be observed in the above table are the absence of any kreatin after the patient had been on the special diet for a matter of four days, showing that there had been no excretion of endogenous kreatin, and, further, the abnormally high kreatinin coefficient (milligrams of kreatinin nitrogen per kilo body weight). According to Shaffer (14) the normal 'kreatinin coefficient' varies between 11·7 and 5·4, although he believes that future research will show that kreatinin coefficients below 7 are normal only for elderly, inactive, poorly developed, or excessively fat subjects. The significance of the kreatin and kreatinin metabolism will be discussed later.

Remarks.

This case presents in a moderately marked degree the most characteristic symptoms of Thomsen's disease, and it would seem that one has to deal with an example of this affection. In some features, however, it differs from many of the previously recorded cases, yet not sufficiently, I think, to justify one in questioning the diagnosis.

As a rule there is a history of heredity, but in my patient, even after careful inquiry, such could not be obtained. In many reports psychical conditions have been described, and in some the myotonia has been said to have been made worse by excitement. This was, as a matter of fact, the case in Thomsen himself and in the members of his family who were similarly affected, and, in consequence, Thomsen (17) considered the affection to be of the nature of a neurosis. In my patient there is absolutely no evidence of a neurotic temperament, unless one may consider his tendency to blush as such, and he emphatically states that excitement has no influence on his condition.

It is a disease which is much commoner in the male sex, and the majority of the patients have been described as unduly muscular, although their strength does not seem to have been proportionate to the size of their muscles. It is said that the muscles are abnormally firm, and that later on they may atrophy. Recently Steinert (16) has stated that a history of muscular dystrophy in the family is as important as that of myotonia itself, and Griffith (6) has reported an instance where there was marked muscular atrophy.

The condition is usually first appreciated by the patient at a comparatively early age [1]—6 to 10 years—and persists throughout life, although Griffith (6) and Herschell (7) have reported cases which have recovered. The condition in Griffith's patient appeared during pregnancy and disappeared after delivery. In some of the recorded examples the ailment has been exceedingly severe, and has been the cause of much inconvenience and misery, as, e. g., the two brothers reported by Angell (1), who, while in the German army, were subjected to cruel punishments on account of their awkward movements: one of these brothers ultimately committed suicide. My patient does not seem to have suffered any great inconvenience so far as his daily work is concerned, but complains mainly of the embarrassment.

Fatigue is often said to make the condition worse, as also excitement and cold, while heat has been observed to lessen the muscular spasm. Fatigue and cold, it should be remembered, induce in healthy muscles a myotonic condition, whereas heat has the opposite effect. So far as my patient is concerned there is only one factor which influences the spasm, viz. rest: it is invariable during the first few moments after a period of rest.

The muscular reactions have been described by Erb (18) in the following manner:

1. The motor nerves show no increase of irritability to mechanical stimulation.

2. The motor nerves to the Faradaic current are quantitatively normal, but with strong currents the contraction lasts much longer than in health.

3. The motor nerves to the galvanic current are quantitatively normal. K. C. C. can be obtained with a current of 5 to 2 milliamperes. If the current be stronger the contraction lasts longer than in health.

4. Mechanical stimulation of the muscles induces contractions more easily than in health, and the contraction often lasts much longer than normally.

5. The Faradaic current applied directly to the muscles gives with a weak current a short momentary contraction, but with a stronger current a contraction which lasts from 5 to 30 seconds.

6. With the galvanic current applied directly to the muscle K. C. C. and A. C. C. are equally easy to obtain, and the contractions last longer than in health. With the stabile application of the galvanic current, well-formed

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[1] Osler and McCrae quote a case diagnosed during infancy and reported by Friis (vol. vi, p. 596).

wave-like contractions are seen to proceed slowly from the kathode to the anode.

It will be remarked that the reactions of the muscles of my patient present several slight differences from those described by Erb. The wave-like contractions could not be elicited, but the majority of observers have not been able to detect them. Erb states that the myotonia induced is almost entirely dependent on the strength of the current, whereas my observations would lead me to conclude that it is conditional more on the duration than on the strength of the stimulation. In my case the muscles did not seem to be more sensitive than in health. In Griffith's patient mechanical stimulation of the muscles did not give rise to the myotonic condition with delayed relaxation.

In many cases the muscles have been microscopically examined during life, and in practically all marked changes have been found. The fibres are unduly large, their diameter being two to three times the normal; the transverse striation is indistinct, the longitudinal fibrillation more marked than in health, and the nuclei of the sarcolemma are said to be increased in number. Occasionally, too, vacuolation of the fibres has been observed, and Schiefferdecker and Schultze (13) have described granulations in the sarcoplasm. Jacoby (8) and Böttiger (4), however, consider the changes described as artifacts, and the former states that he has seen the enlargement of the fibres in normal muscle through contraction occurring after removal, and that, when this is avoided, in the muscles of Thomsen's disease no abnormality is detected. In my patient no histological examination of the muscles has been made.

Perhaps the most interesting chapter in this disease is that dealing with the etiology. Many theories have been brought forward to explain the condition, but as yet not one is satisfactory.

So far only one autopsy has been reported, and in this case no lesion was found in the nervous system, so that the only gross change yet discovered is that in the muscles themselves. From all previous records some change in the muscles would appear to be invariable, and Hale White (18) concludes that no theory can be accepted which does not take these changes, which as previously mentioned are regarded by some workers as artifacts, into consideration. Knoblauch (9), in a recent communication, expresses the opinion that one is not justified in concluding that this muscular change is primary, and not secondary to increased muscular work, until it has been shown that the same lesions are observed in children suffering from the disease, and so far this has not been done. The increased work in overcoming the spasm could no doubt lead to hypertrophy, and, as a matter of fact, the muscles in this condition are usually larger than normal, although their power is not always proportionate to their development. The majority of those who have had an opportunity of examining my patient have considered him unduly strong, though he does not look upon himself as more powerful than the average individual. In hypertrophied muscles the fibres are increased in thickness, and this is just the finding in the muscles of myotonia about which the majority of writers are agreed. Another

important point, and one which is mentioned by Gowers (5), is that muscles cut out during life possess larger fibres than those removed after death, and yet, so far as I can gather from the literature, the muscles taken away from living examples of Thomsen's disease have always been compared with those removed in the post-mortem room. It must be admitted, however, that the figures given by Gowers do not reveal such variations as have been described between healthy fibres and those found in Thomsen's disease, yet this is a point which in my opinion ought not to be lost sight of in a discussion of the muscular changes. And further, so far as the kreatin and kreatinin excretions in our patient are concerned, any question of muscular degeneration must be dismissed. Within recent years the kreatin and kreatinin metabolism have been considered a gauge of muscular efficiency. Kreatin is not found in normal urines unless kreatin is taken in the food, and when endogenous kreatin appears in the urine, it is supposed to be evidence of rapid loss of muscle protein, and occurs in such conditions as acute fevers, exophthalmic goitre, pseudo-hypertrophic muscular paralysis, and during the puerperium, while the uterus is involuting. In our case, then, the absence of kreatin on a kreatin-free diet is distinctly against the idea of there being any degenerative changes in the muscles. Kreatinin excretion, on the other hand, is, according to Shaffer (14) and Spriggs (15), an indication of 'muscle tonus' or of muscle efficiency. The kreatinin excretion is practically constant from day to day, and even during different periods of the same day, for each individual, although varying with the individual. The chief factor which influences the kreatinin excretion is the absolute amount of muscle tissue, whereas the amount of muscular activity is in itself wholly without effect. In a muscle in a normal state of nutrition and development, certain processes which lead to the formation of kreatinin as a waste product are supposed to be going on more rapidly than in a muscle organically weak or functionally inactive. Thus, although the neuro-muscular mechanism should be defective as regards the transmission of impulses from the higher centres, yet if the nerve tracts have no lesion, so that the trophic influence and consequently the potential efficiency of the muscle is unaffected, the kreatinin excretion is normal in amount. It is only when this trophic influence is affected, either from a general condition or diminished irritability, or from a definite lesion in the efferent nerve tracts, e. g. progressive muscular atrophy, and also in primary muscular dystrophy, where, the nutrition being interfered with, atrophic changes take place and the efficiency of the muscle as a machine is decreased, that there is a diminished excretion of kreatinin. It would thus seem from our metabolism experiments that not only are the muscles not degenerate, but that they are extra efficient, and consequently it is not improbable that the increase in size of the muscles may be a true hypertrophy, induced by the excessive work to overcome the spasm, as suggested by Knoblauch.

It would seem, nevertheless, that the majority of authors incline to the view that we have here a disease primarily of the muscular system, and there

are not a few experimental facts in favour of such an idea. The peculiar type of muscular contraction present in this ailment has been observed to be similar to that found in the red muscle of the rabbit, and, recently, Knoblauch (9) has brought forward the theory that in the muscle of man, as in that of the rabbit, are two varieties of fibres—the pale and the red. The pale is narrower, more definitely striated, more easily stimulated, contracts suddenly and relaxes as quickly, and is more readily exhausted ; the red fibres, on the other hand, are broader, possess less definite transverse striation and more distinct longitudinal fibrillation, are less easily stimulated, while the resulting contraction persists for a longer time and relaxes slowly. Schaffer (11), in 1893, described both these types in human muscle, and states that in the slowly acting muscles of the back the fibres are chiefly of the red variety. Julius Arnold, according to Landois and Stirling (10), found in human muscles an extensive distribution of red fibres amongst the pale. Knoblauch believes that there is always an admixture of these two varieties in human muscle, the red being the more highly specialized, and that in the normal individual there is a proper proportion of the two. In the muscles of some individuals the red fibres predominate and the condition of myotonia is produced, while in others the pale are in the majority and myasthenia or myatonia results.

The myotonic type of contraction has been compared to that which occurs under the influence of veratrin, even when the motor end-plates are paralysed by curare. Ringer and Sainsbury (12) carried out some very interesting experiments and showed that an almost similar condition could be brought about in the frog, if its muscles were transfused with phosphate of soda, even if the motor end-plates were paralysed by curare. From these experiments it has been argued that Thomsen's disease is due to some error in muscular metabolism, viz. that katabolism is at first increased, and that there is some delay in the removal of the waste products. In some of Ringer and Sainsbury's myographic tracings there were, in addition to the tonic rigidity, fibrillar contractions which were eliminated by the curare, and so they considered these fibrillar contractions nervous in origin. It is interesting to note that in some of my tracings (Fig. 3) fibrillar contractions are present, a clinical observation also recorded by Ringer and Sainsbury, and these authors conclude that myotonia congenita is a disease in which both the muscles and nerves participate.

The first idea regarding the nature of this malady, and the view that was expressed by Thomsen himself, was that it was psychical, a conclusion based on the neurotic symptoms that the patients often presented. At the present time, however, this theory receives little support. Some writers have considered it due to changes in the nervous system, but the negative findings in the only reported autopsy have not lent support to such an opinion. At the present time no list of supposititious causes would be complete without mention being made of the ductless glands, more especially when all previous theories have failed to satisfactorily explain the condition. Such a hypothesis, too, is quite in keeping with the idea of some error of metabolism, for we know that metabolism and

the ductless glands are intimately associated. According to Biedl (3), H. Lindberg, who was the first to associate tetany with disease of the parathyroid gland, considers that myotonia congenita, as also myoclonus and paralysis agitans, is due to a deficiency of the parathyroid secretion. In this connexion it is interesting to note that Berkeley (2) of New York has reported good results in paralysis agitans with parathyroid gland. Nevertheless, there does not seem to me to be any similarity between tetany, which can be produced experimentally by excision of the parathyroid glands, and myotonia. In the former the contraction of the muscles is painful and tonic in character, and the electrical reactions are markedly altered quantitatively, the muscles being hypersensitive, which is quite the reverse of what occurs in myotonia. It should be remembered, however, that ductless glands may possess more than one internal secretion, and that all may not suffer simultaneously. This would seem to be the case with the parathyroid gland, since excision of the gland induces, in addition to the carpo-pedal spasm, a progressive and fatal emaciation, a condition entirely absent in the clinical picture of tetany in infants. In spontaneous and experimental tetany there has been shown to be an increased calcium excretion, which allows of a relative increase in the economy of K and Na salts, and in this connexion the previously recorded experiments of Ringer and Sainsbury with frogs are exceedingly interesting.

Out of all this mass of experiment and theory are we able to draw any deductions regarding the pathogeny of this rather rare affection? To my mind there is one conclusion that we can draw, and that is that the disease is not one primarily or wholly of muscle, but that in all probability the nervous system plays a not insignificant part in the etiology. In what other way can we explain the different behaviour of the muscles in voluntary and involuntary movements? It has been shown that in voluntary contraction of the abdominal muscles, as in bending, the myotonia develops, whereas during involuntary or reflex action, e. g. defaecation, this peculiar contraction of the abdominal muscles is absent. The same difference is seen in the quadriceps femoris and latissimus dorsi contracting voluntarily and involuntarily. Direct stimulation or electrical stimulation of the muscle brings about myotonia, while contraction of the muscle reflexly, or at least while eliciting the knee-jerk, is normal in character (see tracing, Fig. 6). Moreover, the fact that the condition gradually disappears on a repetition of the voluntary movements, and does not do so on a repetition of the direct or electrical stimulation, negatives the idea of some primary muscle change, as do also the fibrillar tremors, which Ringer and Sainsbury reproduced in their experiments, and which they were able to eliminate by curare. And further, the kreatin and kreatinin metabolism shows that we are not dealing with a degenerate muscle, but with an extra efficient muscle—in short, a hypertrophied muscle—not improbably engendered by excessive work to overcome the spasm. And lastly, mention must be made of the influence of the mental state, which further points to the disease being dominated, at least to a certain extent, by the nervous system.

Since this paper went to the press I have asked Dr. Fraser of Glasgow to try the influence of suggestion in order to see if there was any marked psychical factor in the case. After several attempts it was found possible to induce fairly deep hypnosis, yet, on testing the muscles by voluntary movement and direct stimulation immediately afterwards, the myotonic features were as marked as ever. This would seem to show that in my case at least there is little, if any, neurotic element in the condition.

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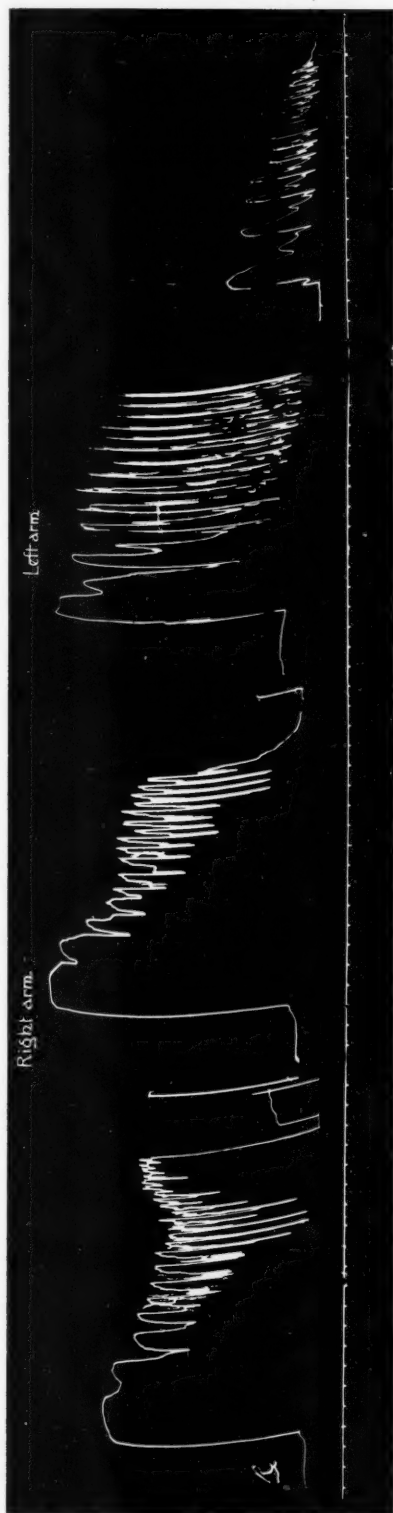
Time 1 sec.

FIG. 1. Myographic tracing of biceps muscle in case of myotonia congenita to show the delayed relaxation after contraction. A balloon, connected with recording tambour, was placed over the biceps muscle and the patient asked to flex and extend his arm as quickly as possible. It will be seen that in the case of the right arm complete relaxation did not occur for 10 seconds.
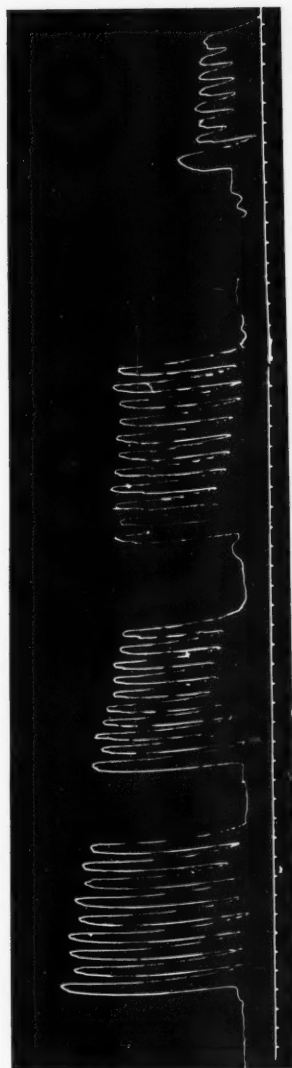

Time 1 sec.

FIG. 2. Myographic tracing of biceps muscle in normal individual to compare with Fig. 1. Note that relaxation occurs at once, but the other movements are not so rapid as in the case of myotonia congenita.
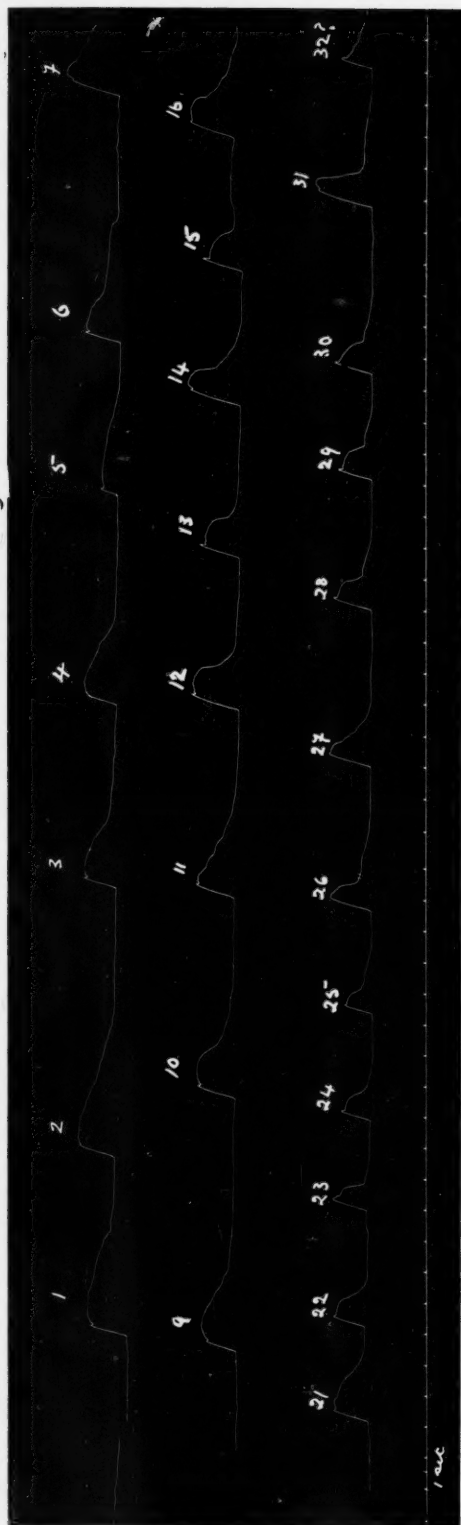
Fig. 3. A series of successive myographic tracings of the extensor muscles of the right forearm. Muscle was directly stimulated by hitting it with the percussion hammer, and contraction recorded by attaching to the middle finger a piece of thread and leading it over a pulley to a spring recording lever. In this way the rise and fall of the hand were registered. Note that the type of muscular contraction does not become normal even after thirty-one successive stimulations.

Fig. 4. Tracing of the normal type of muscular contraction obtained by direct stimulation of the extensors of the forearm to compare with that found in myotonia congenita (Fig. 3).
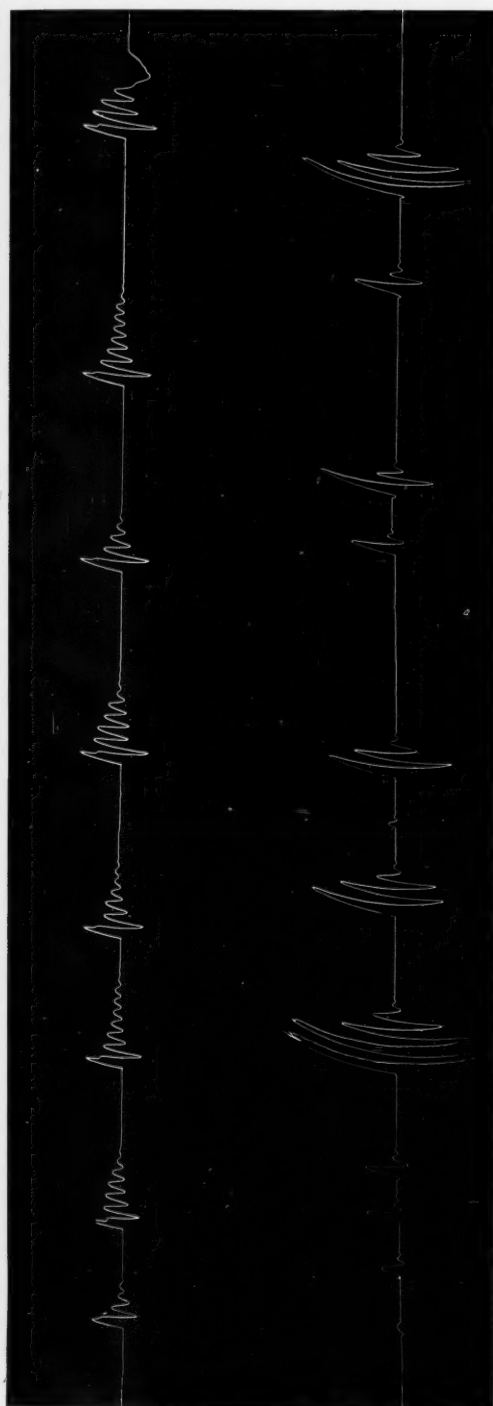
Fig. 5. Tracings of knee-jerks in myotonia and health (upper one). These tracings were obtained by attaching a thread to ankle and leading it over a pulley to a spring recording lever.

Fig. 6. Tracings showing types of muscular contraction induced in myotonia congenita by direct stimulation of quadriceps femoris (D.S.), and by eliciting the knee-jerk (K.J.). The contraction of the muscle on eliciting the knee-jerk is quite normal, while that obtained by direct stimulation shows the typical myotonic characters. These tracings were obtained as Figs. 1 and 2.

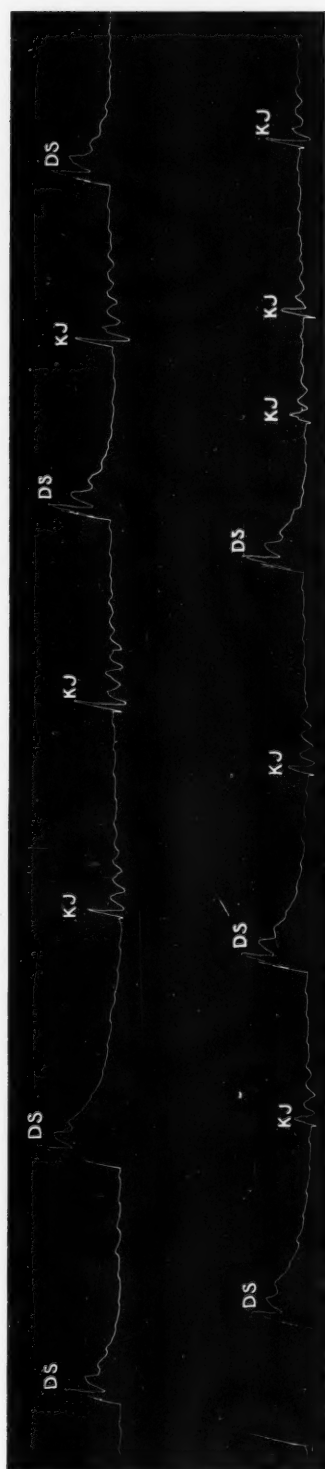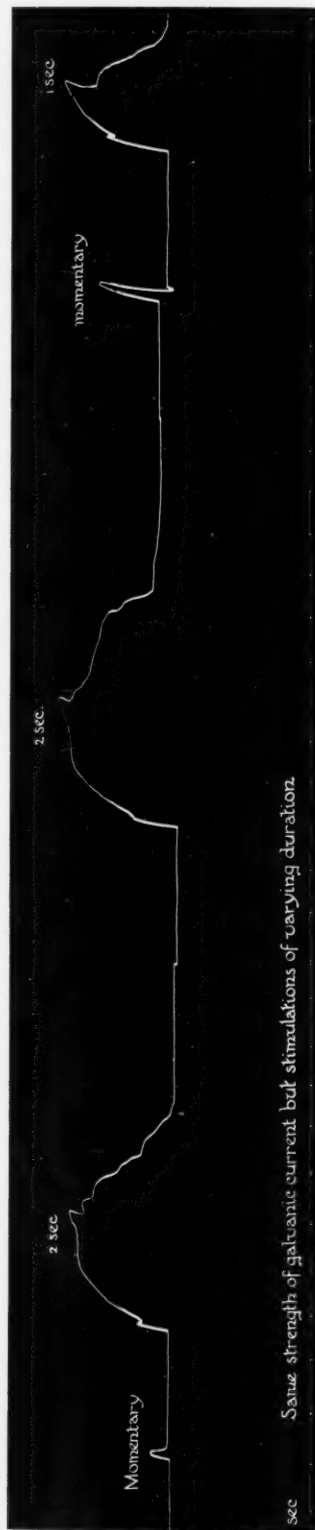FIG. 7. Myographic tracing showing the different types of contraction induced by the galvanic current of constant strength, but of varying duration. The rise and fall of the hand (wrist-jerk) were taken as a gauge of the contraction. Note that with a momentary stimulation a normal contraction results, but that with prolonged stimulation a state of galvanotonus develops and that relaxation is unduly slow.

FIG. 8. Tracing in normal individual with galvanic current to compare with Fig. 7. Note that it does not matter how long the stimulus was applied, but that the only contraction which occurs is the K.C.C.

momentary
stimulation

duration of
stimulation 2 secs

a   b

Same strength of current but with short and long duration.
a-b rebound on cessation of stimulation

Myotonia Congenita

seconds

momentary
stimulation

duration of stimulation
1½ secs

duration of stimulation
2½ secs

Same strength of current but with long and short duration.
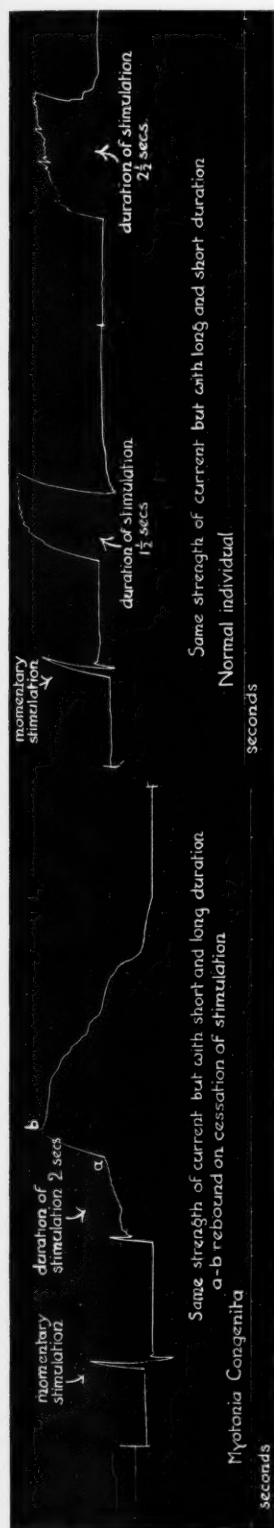
Normal individual

seconds

FIG. 9. These tracings show the effect of a momentary and prolonged stimulation with the Faradaic current of constant strength in myotonia congenita and health. Note that in the former condition (left-hand portion of tracing) a momentary stimulation causes a normal contraction, whereas prolonged stimulation with the same strength of current induces tetanus and slow relaxation, and that on removal of the stimulus there occurs a marked rebound, a condition which Sherrington has observed in post-mortem rigidity in animals. Compare the sudden relaxation after cessation of the stimulation in the control (right-hand portion of tracing). These tracings were obtained in the same manner as Figs. 1 and 2.

1. Normal Individual. 2 and 3. McDonald (Myotonia Congenita). a-b latent period
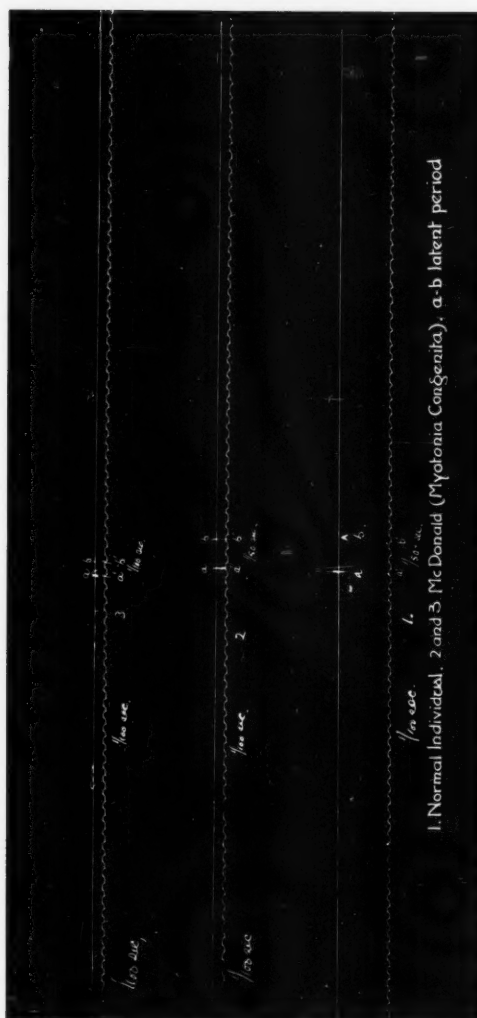
FIG. 10. Tracings showing latent period (a–b) in health (1) and myotonia congenita (2 and 3). Note that latent period is not prolonged and that with slight stimulus relaxation is much slower in health than in the condition of myotonia congenita.

A FURTHER NOTE ON OCHRONOSIS ASSOCIATED WITH CARBOLURIA

By A. P. BEDDARD and C. M. PLUMTRE

With Plates 35–37

In a previous volume of this Journal one of us (A. P. B.) (1) reviewed the twenty cases of ochronosis then on record, and strongly supported the view that a chronic intoxication with carbolic acid, as a cause of ochronosis, is second only to alkaptonuria. Almost at the same time that the paper was published Poulsen (2) gave a very full and detailed account of nine new cases; in six of them the condition was associated with alkaptonuria and in three with the application of carbolic acid to ulcerated legs. Another case associated with the use of carbolic oil is now being added. Before considering the bearing of these ten new cases upon the opinions previously expressed, this additional case may be described.

John P., aged 73, was admitted into a London Infirmary suffering from pneumonia. When it was realized that he was a case of ochronosis, he was too ill to give more than a very few details of his history. He had been in the army as a young man, and when in India had been troubled with ulceration of both legs. Although some of the ulcers had healed, from time to time others had formed; his legs had never been free from ulceration ever since they were first affected. For at least forty years he had treated the ulcers every day with carbolic oil. For about the last ten years pigmentation of his ears, eyes, face, and hands had been noticed by himself and his friends. He had occasionally seen that his urine was a very dark and peculiar colour in the chamber, but had paid no special attention to it. For about a week before admission he had been too ill to dress his ulcers with carbolic oil.

The ulceration of both legs was deep and extensive. The left shin was ulcerated nearly down to the bone throughout its entire length. There were in addition four deep ulcers on the left leg, one being on the thigh. The right leg was less extensively affected. There were several scars of healed ulcers above as well as below both knees. The veins were not varicose in either leg. From the character of the scars and ulcers and from the appearance of the aorta at the autopsy, it was almost certain that the ulceration was syphilitic. The man denied having ever been treated by a doctor for the ulceration.

The skin of the forehead, trunk, and limbs excepting the hands was very pale. The skin of the face below the level of the eyes and of the upper part of the neck was of a deep brown colour (Plate 35).

The ears were typical. The concha and anti-helix were of a slaty blue colour; the lobule and helix were brownish.

The nose was of a vivid light blue colour at the lip; as also was the adjoining part of the septum.

The eyes showed the usual symmetrical patches of brown pigment, roughly triangular in shape and lying in the horizontal plane. When looked at from a little distance the pigment appeared to reach the margin of the cornea, but with a magnifying glass it could be seen to be separated from the cornea by a fine line of white sclerotic.

The hands were remarkably blue. Plate 36 shows the distribution of the colour on the palmar surface. The blue discoloration extended round on to the dorsum of the first and little fingers. The knuckles showed a slate-blue discoloration when the hands were clenched; as did the extensor tendons on the backs of the hands. The nails showed the same light blue colour as the palms, together with scattered patches of brown pigment. It may be definitely stated that the light blue colour of the nails, hands, and nose was not caused by cyanosis, since it was unaffected by pressure.

The feet were much less pigmented than the hands. Nevertheless some blue colour was visible in the extensor tendons, the nails, and the soles.

The joints of both hands showed changes due to multiple osteo-arthritis. None of the larger joints appeared to be affected.

Treatment. The patient was given the usual remedies for pneumonia. He took nourishment fairly well, consisting of about three pints of milk a day, together with beef tea. Hot boracic fomentations were applied to the ulcers.

The urine which was examined consisted of that passed on two consecutive days after he had not had any carbolic oil applied for about ten days. The urine was of a light amber colour, acid, and had a sp. gr. 1·010. It contained a trace of albumin; blood and bile were absent; it did not darken on standing; it gave no colour reaction with either caustic potash or a solution of ferric chloride. It did not reduce either Fehling's solution or an ammoniacal silver solution in the cold; nor did it give a positive reaction with Nylander's solution. The distillate from the acidified and steam-distilled urine gave a very faint trace of precipitate with bromine-water. Homogentisic acid was looked for both by the method of Garrod and by that of Orton and Garrod, with negative results.

A partial autopsy was performed eighteen hours after death. It was only with the greatest difficulty that permission could be obtained for even a partial examination; it was only after the most pressing and urgent representations that any pathological material was allowed to be removed. One eye-ball and half of the sternum together with the attached costal cartilages were sent to the Museum of St. Bartholomew's Hospital. The other half of the sternum and eye-ball, the ascending aorta, the right patella and internal semi-lunar cartilage, and the larynx with the upper part of the trachea are in the Museum of Guy's Hospital. They are shown in Plate 37. Unfortunately this material was placed in a formalin solution which partially bleached some of the brown pigment. Alcohol to which a small quantity of ozonic alcohol was added restored the black colour to a considerable extent, but not wholly. The coloured drawings were made from the material as it now exists; the pigmented structures at the autopsy were much darker.

The lungs showed old adhesions on the left side, and an oedematous pneumonia in both lower lobes. The *heart* was large; the *spleen* soft; the *liver* and *pancreas* appeared to be healthy. The *kidneys* were smaller than normal, red, and finely granular on the surface. The smaller *arteries* were much thickened

The aortic valves and ascending aorta were very atheromatous. There were numerous ulcers and a localized aneurysmal dilatation in the ascending aorta. The structures were extensively discoloured by slate-blue and brown pigmentation; the colour was deepest where the vessel was most diseased. Numerous calcareous plates were of a light green colour which disappeared completely and permanently in the formalin and is not represented in the plate.

The right knee-joint was the only large joint which could be opened. It

was quite free from osteo-arthritis. The colour and appearance of the internal surface were exactly like that of a really well polished black boot. The patellar tendon and semi-lunar cartilages were dark brown. The interior of the sterno-clavicular joint was also black.

The cause of the ochronosis in twenty-three out of the thirty recorded cases is known; fourteen have been associated with alkaptonuria and nine with the use of carbolic acid. Four of the former and four of the latter have come to autopsy; in every case the post-mortem appearances have been the same.

The number of carbolic cases certainly excludes coincidence; the autopsies show that they are true ochronosis and the full examination of the urine in some of them proves that they are not, as has been suggested, alkaptonuric cases in which the peculiar abnormality of the urine has been overlooked. Further, if a slow and prolonged absorption of carbolic acid is ever followed by this pigmentation, it would be fair to argue, if the colour lessened or disappeared after the discontinuance of the carbolic acid, that this intoxication had been the cause of the ochronosis. This has actually taken place in the case of Ellen B., who was previously reported by one of us. This woman has not had carbolic oil applied to her ulcers for more than two years. She has recently been seen again (January, 1912). The pigmentation of the eyes has so far disappeared that it is only in a strong light and with the greatest difficulty that any trace of it can now be seen. The same is to a less extent true of the ears. It may confidently be anticipated that in another two years' time it will no longer be possible to demonstrate clinically that the woman has been a case of ochronosis.

Of the seven remaining cases, in five no abnormality of the urine is known; but it is necessary to add that in them the urine was either not obtained or not specially tested. There still remain therefore only two cases of ochronosis which are known to have been due neither to alkaptonuria nor to carbolic acid.

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2. Poulsen, *Ziegler's Beiträge z. path. Anat. u. z. allgem. Path.*, 1910, xlviii. 346.

DESCRIPTION OF FIGURES.

PLATE 35. Case of ochronosis showing the pigmentation of the sclerotics, ears, and face.

PLATE 36. The palmar surface of a hand of the same case.

PLATE 37. The ascending aorta, half of the sternum together with the attached costal cartilages, the larynx with the upper part of the trachea, the right patella and internal semi-lunar cartilage from the same case.
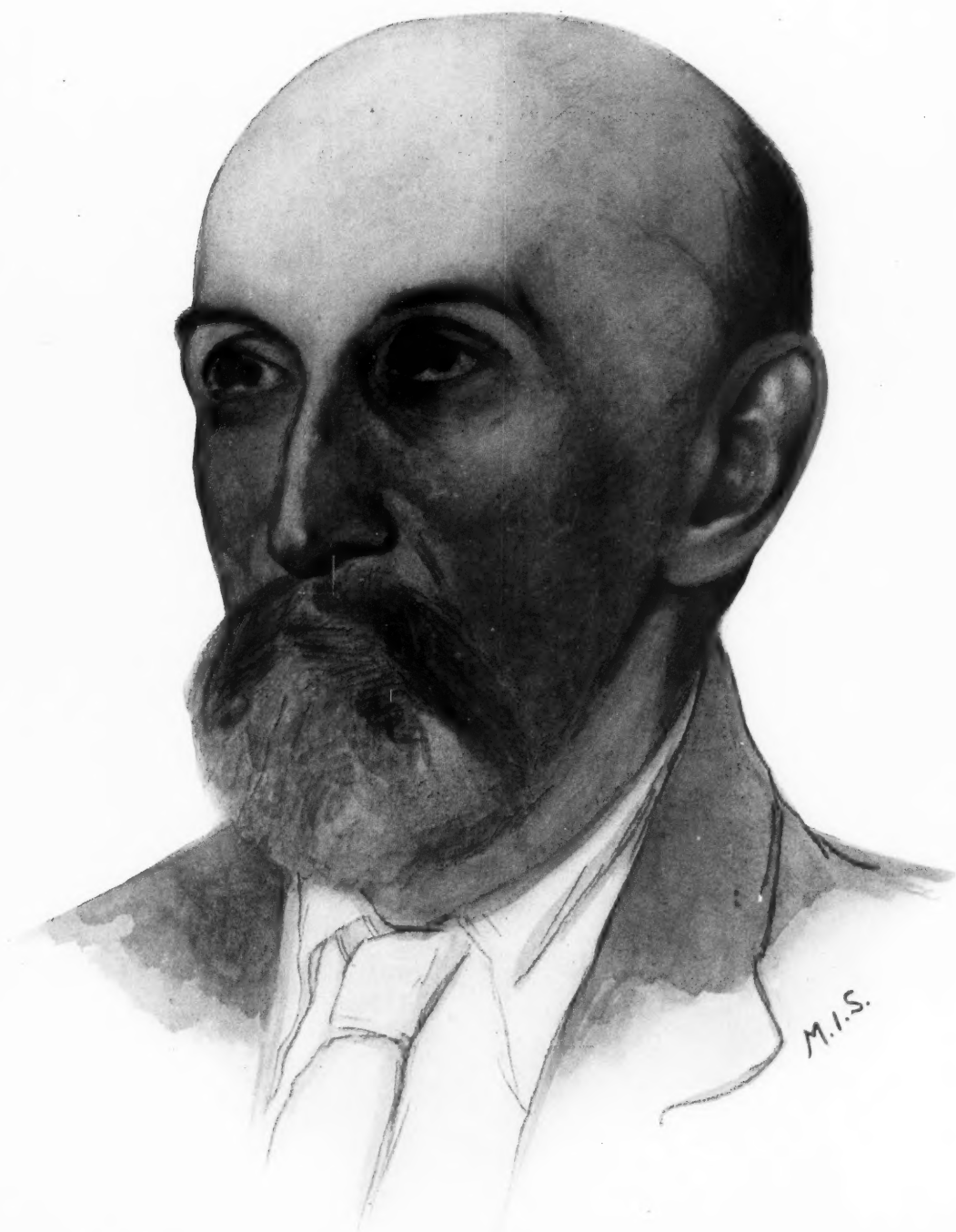
M.I.S.

CRITICAL REVIEW

THE SENSITIZED VACCINE OF BESREDKA

By M. H. GORDON

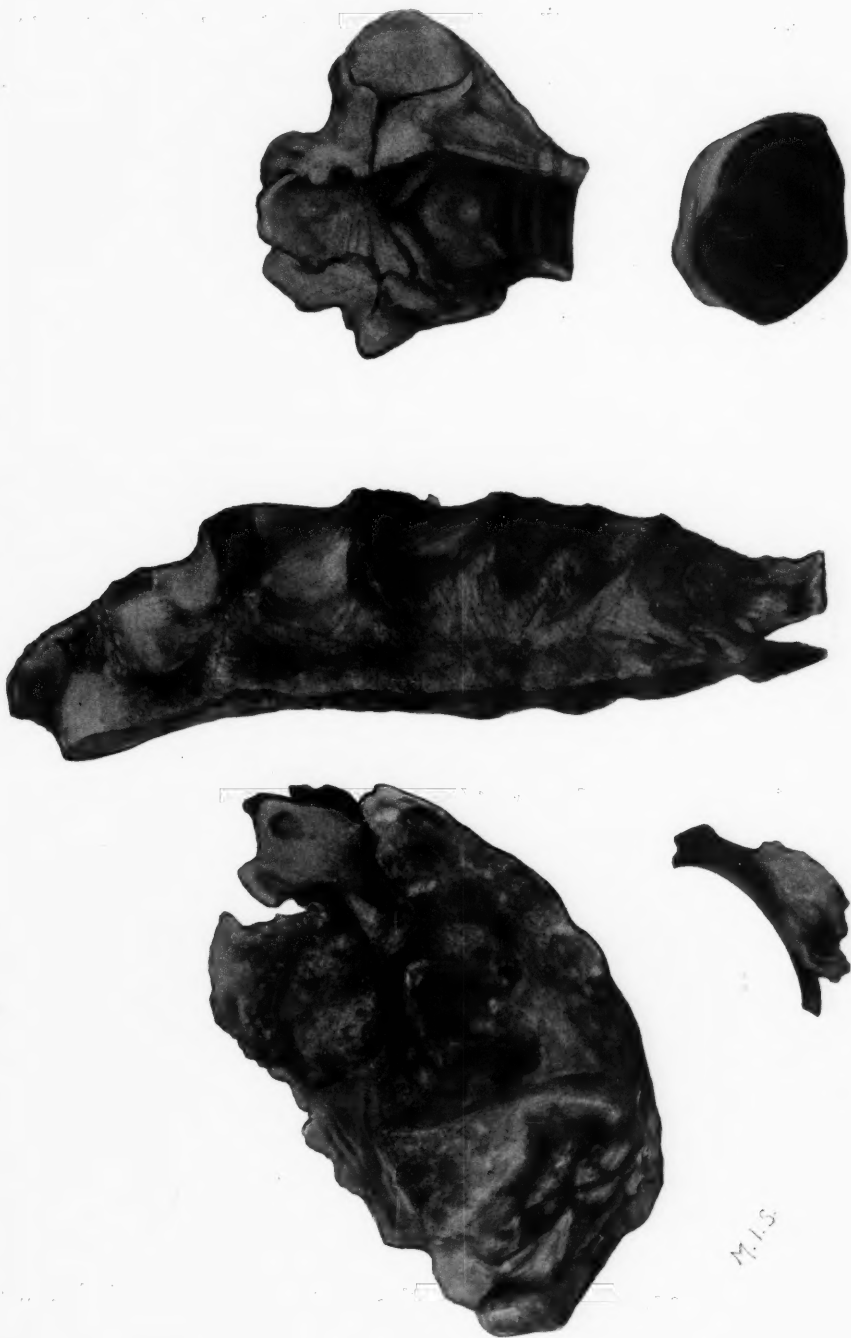At the present time, two principal methods are in general use for producing immunity to a given pathogenic micro-organism. Either the animal is actively immunized by inoculating it with a vaccine of the killed micro-organism, or of its products; or it is immunized passively by injecting serum containing specific antibody already elaborated by another animal in response to such vaccination. In the first case the animal is stimulated to produce its own antibody, and in the second the antibody elaborated by another animal is made use of. Each of these methods has its advantages, and each its shortcomings.

The immunity obtained by active immunization lasts as a rule for several months. The drawback is that immediately following on the injection there ensues a period of variable duration known as the negative phase, during which resistance to infection is actually lower than normal. Moreover, if the dose is large, the inoculation is liable to be attended by considerable disturbance, either local or general, or both.

Passive immunity, on the other hand, has the advantage that it is rapidly attained—immediately if the antibody is administered intravenously, and within twenty-four hours if injected by the subcutaneous route. The drawbacks are as follows: In the first place the immunity does not last for longer than eight to fourteen days. Secondly, in the human subject, when a large amount of horse serum has to be given in order to supply the necessary antibody, the subcutaneous reception of this amount of fluid is liable to be attended with considerable inconvenience, not to say pain. Thirdly, such injection of horse serum is liable to be followed by the group of disagreeable symptoms known as the serum sickness; and fourthly, the patient may become hereafter hypersensitive to horse serum. It is clear that there is room for improvement in our present methods of producing immunity.

Lorenz, in 1892, in order to protect pigs against swine erysipelas, was one of the first to combine the two methods of active and passive immunity in one by administering at the same time vaccine and serum as a prophylactic.

The value of the combined method was examined experimentally in the case of plague by Calmette and Salimbeni. It was found that the immunity thus produced was of longer duration than when immune serum alone was given,

but considerably less than when vaccines were given alone. The duration of the immunity was seven to eight weeks, as against four, five, or six months with the vaccine alone. Beinarowitch, who also investigated the same point in regard to plague, came to the conclusion that the aptitude to elaborate active immunity, and the duration of this immunity, are in inverse ratio to the quantity of immune serum injected before inoculation with the bacilli. Pfeiffer and Friedberger, investigating immunity to the cholera vibrio in a similar sense, gave to one set of animals doses of cholera vibrio sufficient to cause antibodies to appear in their serum. To another series of animals they gave the same doses of cholera vibrio with the addition of increasing doses of anticholera serum. It was found that the more the specific antibody was added, the less the animals elaborated this substance themselves, and a point was eventually reached at which they elaborated no more ; though the same dose of vibrio was given as before.

It appears, then, that, apart from questions of serum sickness and anaphylaxis, the administration of serum tends to interfere to some extent with the production of immunity in response to treatment by vaccine.

BESREDKA'S METHOD.

Besredka bases his method on the discovery of Ehrlich and Morgenroth, that every cell when brought in contact with its specific antibody fixes it to the exclusion of every other substance which may be present.

Applying this principle to the present purpose, Besredka uses the vaccine to abstract specific antibody from an immune serum. He then gets rid of the serum, and uses the combination of vaccine and antibody as sensitized vaccine.

The process of sensitization is carried out as follows : An emulsion of the micro-organism is made in saline and counted. This emulsion is next brought in contact with serum from an immunized animal, and the serum and emulsion are left in contact for twelve hours at the room temperature. During this time the bacillary bodies attract to themselves the specific antibody present in the immune serum. At the end of the twelve hours the bacillary bodies have deposited at the foot of the tube. The serum is now pipetted off and replaced with saline. The tube is well shaken and centrifuged for a few minutes until the bacillary bodies have again sunk to the bottom. The saline is then pipetted off and replaced by more, and the centrifuging repeated. In this way all traces of serum are removed and a pultaceous deposit of bacterial bodies with their specific antibody attached is obtained. This is the so-called sensitized vaccine of Besredka.

There are a few practical points that may be mentioned.

1. The serum must contain definite antibody to the micro-organism. Before using a serum Besredka satisfies himself of the presence of agglutinin specific for this micro-organism.

2. He uses as little antibody as is compatible with sensitization.

3. It is well to count the emulsion before bringing it in contact with the serum. In this way difficulty due to agglutination is avoided.

4. It is convenient to carry out the whole process in a graduated centrifuge tube, and it is advisable to complete it in one day.

Those who are quite satisfied with our present knowledge of immunity would consider, perhaps, that there is no need to kill the bacilli after sensitization. Living vaccines sensitized in the way described have as a matter of fact been given, as will be described later. Most people, however, prefer to take no risks, and it may be mentioned that in the case of killed vaccines Besredka prefers to kill the micro-organisms after sensitization. This may be effected either by adding 0.5 per cent. phenol, or by heat.

Sensitized vaccine appears to keep well, provided the excess of saline is pipetted off. Besredka has kept one as long as six months without loss of power.

The Effect of Sensitized Vaccines.

I. The effect of sensitization in reducing the toxicity of a vaccine.

In one of his earliest papers on the subject Besredka gives a remarkable instance showing the effect of sensitization in this sense.

Cultures of plague bacilli retain some of their toxicity even when killed by heat. Thus, Haffkine's plague prophylactic, which consists of a broth culture of *B. pestis* heated to 70° C., kills a mouse in a dose of $\frac{1}{10}$ c.c. (Wourtz and Bourges). Besredka found that heated agar cultures were equally toxic, $\frac{1}{10}$ to $\frac{1}{15}$ c.c. of a forty-eight hours agar culture killed by heat producing a fatal result in a mouse in forty-eight hours with symptoms of intoxication. Now, after sensitization, Besredka found that he could inject two whole heated agar cultures, i.e. 20–30 times the dose previously toxic, into a mouse sub-cutaneously without producing any symptoms at all.

II. The value of sensitized vaccines for producing immunity to various pathogenic micro-organisms.

Plague. The effect of sensitization in reducing the toxicity of plague vaccine has just been referred to.

As regards rapidity of onset of the immunity, mice injected with sensitized plague vaccine withstand a fatal dose of living plague bacilli forty-eight hours after vaccination. The immunity lasts in the guinea-pig for a month and a half, and in mice for four to five months.

Cholera. Guinea-pigs injected with a dose of sensitized cholera vaccine become immune to a fatal dose of living cholera vibrio twenty-four hours later. The immunity lasts for over five months.

Typhoid. Guinea-pigs injected with a dose of sensitized typhoid vaccine withstand a fatal dose of living typhoid bacilli twenty-four hours later. This immunity lasts for over five months.

Paladino Blandini made an exhaustive experimental investigation of the

comparative values of various typhoid vaccines. He tested in this way no less than seventeen different vaccines as follows :—(1) Cultures living and virulent in broth ; (2) cultures living but attenuated by growth at 40° C. for three days ; (3) the vaccine of Pfeiffer and Kolle ; (4) the vaccine of Wright and Semple ; (5) the toxin of Chantemasse ; (6) the toxin of Werner ; (7) the toxin of Rodet, Lagriffoul, and Wahly ; (8) filtered peritoneal exudate ; (9) typho-nucleo-albumin ; (10) the extract of Macfadyan and Rowland ; (11) the extract of Brieger and Mayer ; (12) the toxin of Balthazard ; (13) the extract of Shiga ; (14) Wassermann's extract ; (15) Berne antityphoid serum ; (16) the extract of Jez ; (17) the vaccine of Besredka. As a result of this comparative trial he concluded in favour of the vaccine of Besredka, which 'not only has the advantage of conferring immunity within twenty-four hours, but ought to be considered the best of all the immunizing procedures in view of the fact that it gives rise to no reaction local or general, that it does not predispose to infection, and that it confers on animals an immunity more durable than that obtained by all the other methods known'.

More recently Metchnikoff and Besredka, having shown that chimpanzees develop typhoid fever when they are infected by mouth with *B. typhosus*, tested the comparative values of an emulsion of typhoid bacilli killed by ether and autolysed (Vincent), and of living typhoid bacilli sensitized, for protecting chimpanzees against infection. They found that while Vincent's vaccine failed to protect, Besredka's vaccine succeeded equally well as a previous attack of typhoid in protecting the chimpanzee against typhoid infection by the alimentary canal.

During the past few months Broughton Alcock, working in M. Metchnikoff's laboratory, has taken the matter a stage further ; and has injected forty-four human beings with living typhoid-sensitized vaccine. He gave them subcutaneously two injections consisting first of 1 c.c. of a 1 per cent. dilution of a twenty-four hours' peptone-free agar culture of typhoid, followed eight to ten days later by 2 or 3 c.c. of the same. His observations demonstrated the harmlessness of this sensitized vaccine of living typhoid bacilli ; and showed further that the living typhoid bacilli, when sensitized, produced less local and general reaction than the same dose of typhoid bacilli killed, but unsensitized. He informs me that cultures from the urine and faeces showed that no living typhoid bacilli were excreted in these materials by the patients who had been injected with the living sensitized vaccine.

Dysentery. Owing to the great toxicity of the micro-organism, immunization of laboratory animals against bacillary dysentery by means of heated cultures is a matter of some difficulty. The immunity does not appear before twelve to fifteen days, if it appears at all ; for about 40 to 50 per cent. of the mice die in course of vaccination.

During the period that elapses between the injection and the appearance of immunity resistance to infection is lower than normal. The immunity, moreover, does not endure for over four to six weeks.

Similar results were obtained by Dopter when he used autolysed dysentery vaccine. None of these methods of producing active immunity could be recommended for use in the case of human beings in face of an epidemic.

By sensitizing the vaccine, however, Dopter succeeded in overcoming all difficulties. In the first place, he found that the mice would now stand a dose of vaccine equivalent to 100 times the fatal dose of ordinary heated culture, and that without loss of weight or any apparent disturbance of health. He concluded as follows :

1. The vaccine by sensitized bacilli is in no degree toxic. It produces no reaction, either local or general.

2. The mice thus treated acquire an antidysenteric immunity in about four to five days.

3. During the incubation period of this immunity the animal is no more sensitive than a control to a fatal dose.

4. The immunity thus obtained lasts for at least four months and a half.

In view of these encouraging results on animals Dopter thinks that the sensitized vaccine is eminently suitable for trial in human beings in the face of an outbreak.

Streptococcal infections. Levy and Hamm tried sensitized streptococcal vaccine in cases of puerperal sepsis with encouraging results. Marxer, having first of all satisfied himself that rabbits after injection with sensitized streptococci became capable twenty-four hours later of withstanding several times the fatal dose of virulent streptococci, tried the same vaccine as a curative; but his results were disappointing. The sensitized vaccine was superior to the vaccine of streptococcus killed by galactose (which Marxer himself had introduced), and also superior to vaccines of streptococcus killed by heat or by tricresol, as shown by the longer life of the animals; though they eventually succumbed.

Pneumococcal infection. The experimental work of Levy and Aoki showed that vaccination by the intensive method of W. Fornet and M. Müller, in which increasing doses of vaccine are given on three successive days, was particularly efficacious for protecting rabbits against the pneumococcus. They found that ten to seventeen days after vaccination by three successive and large doses in this way the rabbit would withstand even 10,000 times the dose of living pneumococcus fatal to a control animal.

On comparing the values of pneumococcus vaccine unsensitized and sensitized respectively, they found that the immunity produced by sensitized vaccine was both more rapidly attained and of a more solid character.

Encouraged by the success of Levy and Hamm with sensitized streptococcal vaccine in puerperal sepsis, they investigated the curative value of sensitized pneumococcus vaccine. On injecting into one part of a rabbit 100,000 living virulent pneumococci, and into another part of the same animal a dose of sensitized pneumococci, they were able to obtain either survival of a certain duration, or

complete survival. The result depended chiefly on the dose of sensitized vaccine used. Thus while a dose of 1–2 c.c. was not sufficient to save the animal, with 4 c.c. of sensitized vaccine they protected two animals out of three, and with 6–8 c.c. they saved all the animals. The result with non-sensitized vaccine was not so good. They concluded that with sensitized pneumococcus vaccine immunity in rabbits follows quicker and more surely than with non-sensitized vaccine.

Tubercle. Fritz Meyer investigated the effect of a vaccine of sensitized tubercle bacilli both on experimental animals and on persons suffering from tuberculosis. He sensitized his emulsion of tubercle bacilli with the anti-tuberculous serum of Höchst, which is both agglutinating and precipitating, fixes complement in the presence of tubercle bacilli, and neutralizes tuberculin and renders it harmless for the tuberculous guinea-pig.

His experiments on animals showed that the sensitized tubercle bacilli were tolerated by tuberculous guinea-pigs in doses five times superior to non-sensitized bacilli. These animals also withstood repeated doses of the sensitized bacilli, whereas they succumbed generally when non-sensitized bacilli were injected in the same way.

The treatment with sensitized tubercle vaccine prolonged the life of the tuberculous guinea-pigs considerably, and in early cases seemed to retard the development of the disease. For instance, although they eventually died, he succeeded in keeping tuberculous guinea-pigs alive for nine months after the death of the controls, which had succumbed in eight weeks. In man the sensitized tubercle vaccine on subcutaneous injection is rapidly absorbed, and the local reaction is minimal.

Meyer tested sensitized vaccine in forty-seven cases of tuberculosis, with amelioration in forty. The best result was with localized tuberculosis—e.g. fistulas and abscesses which had resisted previous treatment healed rapidly. The results were less favourable with tuberculous affections of the bones, joints, and eyes. In pulmonary tuberculosis the fever and sweating and other symptoms due to intoxication were improved, but there was no effect on the lesion, nor on the number of tubercle bacilli in the sputum.

Rabies. It is interesting to note that the method has also been applied by A. Marie with success in the case of a disease due to an ultra-microscopic micro-organism, e.g. rabies.

In preparing the vaccine an emulsion of ' fixed virus' is mixed with anti-rabic serum, and after contact for twenty-four hours, the serum is removed by washing with salt solution. The mass thus obtained contains the rabic virus sensitized by its specific antibody.

Marie found that this vaccine had parallel properties to the sensitized vaccines referred to previously. It is non-toxic, and can be injected into the brain without producing any bad effect on the animal. Its immunizing action is rapid : while with the Pasteurian vaccination it is necessary to wait a fortnight after a long series of injections before proving the immunity of the animal successfully,

with the method of sensitized vaccine the animal passes this test three days after receiving the vaccine. The immunity is also durable.

Marie has incorporated the method with success in the treatment of persons bitten by animals affected with rabies.

Poliomyelitis. Levaditi and Landsteiner have shown that the same method is successful in protecting monkeys against this disease.

From the experimental evidence, then, it would seem that the results obtained on animals with the method of Besredka are very encouraging. Besredka regards the main action of sensitized vaccine as being to activate and accelerate the work of the leucocytes. Whatever may be the correct explanation, there can be no doubt that from the laboratory point of view the method forms an advance on previous methods of producing immunity. While its value is undoubtedly greatest in a preventive sense, it appears to have some curative action in animals—a point which suggests that perhaps the method of treatment by sensitized vaccine is worthy of a more extensive trial clinically than it has yet been given.

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ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND. MINUTES OF THE PROCEEDINGS OF THE SIXTH ANNUAL GENERAL MEETING.

THE SIXTH ANNUAL GENERAL MEETING was held at Glasgow on Thursday, April 18, and Friday, April 19, 1912, in the Physiological Class-room, Glasgow University, by permission of the University Court and of Professor Noel Paton.

On Thursday, April 18, in the unavoidable absence of the President and Treasurer, the chair was taken by the Secretary.

The minutes of the previous meeting were confirmed.

The President, Officers, and Members of Committee for the ensuing year were elected :—

President : Dr. G. S. Middleton.

Treasurer : Dr. Hale White.

Secretary : Dr. Herringham.

Members for England :—
Dr. Judson Bury.
Dr. William Collier.
Professor Wardrop Griffith.
Dr. H. P. Hawkins.
Dr. F. J. Poynton.
Professor R. Saundby.

Members for Scotland :—
Dr. Barclay Ness.
Dr. William Russell.
Professor Stalker.

Members for Ireland :—
Dr. William Calwell.
Professor James Craig.
Dr. A. R. Parsons.

The President then took the chair.

He proposed a vote of thanks to the retiring President, Sir Thomas Barlow, Bt., P.R.C.P., which was carried, described the arrangements made for the meeting, and thanked those non-members who had so greatly co-operated in making them.

The election of the candidates nominated by the Committee was then carried out. All the candidates were declared elected.

As Honorary Member—

Sir Donald MacALISTER, K.C.B., M.D., D.C.L., LL.D., F.R.C.P., Principal of the University of Glasgow.

As Members—

BATTEN, Fredk. E., M.D. Cantab., F.R.C.P., 33 Harley Street, W. Physician, Great Ormond Street Hospital ; Physician to Out-patients, Queen Square Hospital.

CROOM, David Halliday, M.D. Edin., F.R.C.P. Edin., 17 Alva Street, Edinburgh. Assistant Physician, Leith Hospital; Clinical Tutor, Royal Infirmary.

EDGECOMBE, Wilfred, M.D. Lond., F.R.C.S., M.R.C.P., Victoria Avenue, Harrogate.

ELLIOTT, Thomas Renton, M.A., M.D. Cantab., M.R.C.P., University College Hospital, W.C. Fellow of Clare College, Cambridge; Assistant Physician, University College Hospital; Beit Research Scholar.

FOGGIE, William Edward, M.A., M.D. Edin., 4 Airlie Place, Perth Road, Dundee. Physician, Dundee Infirmary, and to Royal Hospital for Incurables, &c.

FORDYCE, A. Dingwall, M.D., F.R.C.P. Edin., 8 Manor Place, Edinburgh. Extra-Physician to the Royal Hospital for Sick Children.

HARRINGTON, Archibald W., M.D. Glasg., 9 Burnbank Terrace, Glasgow. Assistant Physician, Glasgow Royal Infirmary.

HOUSTON, Thomas, M.D., R.U.I., 95 Great Victoria Street, Belfast. Assistant Physician in charge of Department of Haematology and Vaccine Therapy, Royal Victoria Hospital; Physician, Forster Green Hospital for Chest Diseases; Pathologist, Ulster Hospital; Joint Lecturer on Medical Jurisprudence.

HUME, William Errington, M.B., B.C. Cantab., M.R.C.P., 25 Ellison Place, Newcastle-on-Tyne. Physician, Royal Victoria Infirmary; Physician, Northumberland and Newcastle Sanatorium.

JACK, William R., M.D., B.Sc., 43 Lansdowne Crescent, Glasgow. Assistant Physician, Western Infirmary, Glasgow.

LISTER, Thomas David, M.D. Lond., M.R.C.P., F.R.C.S., 50 Brook Street, Grosvenor Square, W. Physician to the Mount Vernon Hospital and the Royal Waterloo Hospital.

MACKENZIE, Ivy, M.A., B.Sc., M.B. Glasg., 101 Hyndland Road, Glasgow. Director, West of Scotland Asylum Research Institution; Pathologist, Royal Hospital Sick Children.

McNEIL, Charles, M.D., M.R.C.P. Edin., 4 Torphichen Street, Edinburgh. Extra-Physician to Royal Hospital for Sick Children.

MILLER, Reginald, M.D. Lond., M.R.C.P. Lond., 53 Queen Anne Street. Assistant Physician, St. Mary's Hospital; Physician, Out-Patients, Paddington Green Children's Hospital.

RANKIN, John Campbell, M.B., R.U.I., 38 University Road, Belfast. Physician in Charge, Electrical Department, Royal Victoria Hospital; Physician, Forster Green Hospital for Consumption; Physician, Abbey Sanatorium.

RIPPMAN, C. H., M.D. Cantab., 1 Weymouth Street, W. Medical Registrar, Guy's Hospital.

TIDY, H. Letheby, M.B., B.Ch. Oxon., M.R.C.P., 39 Devonshire Place, W. Physician, Great Northern Hospital; Medical Registrar, London Hospital.

The Treasurer's accounts were presented by the Secretary,

<div style="text-align:center">

Showing a cash balance of   £147 19 5
And a deposit credit of   400 0 0

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The accounts were adopted.

The President then referred to the selection of a place for the next Annual Meeting. He pointed out that the International Medical Congress of 1913 would absorb the work, the time, and the money of members, and asked the Meeting to consider whether it would be advisable to hold a meeting next year.

After considerable discussion, it was resolved, in order to comply with the rules, that a meeting should be held for business purposes alone, and that the time and place of its assembly should be left to the Executive Committee.

An invitation was read from the Chancellor and Provost of the University of Dublin, on which it was resolved that the President be requested to represent the Association at the Dublin Bicentenary. The President expressed his willingness to accept the task.

The scientific business of the Meeting then began.

1. Dr. A. G. Gibson related a case of retrogressive tuberculous meningitis.

A girl of 4 years was taken ill with the usual symptoms. Lumbar puncture was performed. Tubercle bacilli were found in the fluid. She recovered. Some time (a few months) later she died of broncho-pneumonia. At the post-mortem there were flattened tubercles in the usual sites, and thickening of the meninges, scattered fibrous patches in lungs, scattered tubercular deposits in spleen, atrophic miliary tubercles in liver, and a caseous lesion in the kidney. Microscopically the tubercles in the brain were atrophic. From the eighth to the fifteenth week she was treated by gradually increasing doses of tuberculin, which seemed to have a certain effect.

Dr. Drummond remembered a man of 20 who had two separate attacks with cerebral symptoms, and within the year an attack of abdominal tuberculosis, of which he died. Signs of past meningitis were found at the post-mortem.

Dr. Tyson referred to a paper by Dr. Bowles, and thought that he himself had seen recoveries.

Sir Clifford Allbutt had twenty-five years ago published a case which he believed to have been of this nature, but had never seen one since.

Professor Hill Abram thought he had seen a case of recovery from tuberculoma of the cerebellum under the use of tuberculin. He asked whether the presence of acid-fast bacilli should be taken as sufficient evidence of tubercle.

Dr. French asked if any one could throw light on the causation of the small fibrous nodules (mustard-seed size) sometimes found in the spleen.

The President thought he had seen cases of recovery, and mentioned a case of which Sir William Gairdner held the same opinion.

Dr. Gibson thought that in expert hands microscopic evidence was reliable, and added that the diagnosis of diphtheria was accurate in 95 per cent. of cases, though resting on exactly the same class of evidence.

2. Dr. Fawcett related the case of a man of 38, who, since 10 years of age, had had attacks of vomiting, and after one such attack, died. The specimen was sent up to Guy's, when it was found to be a very dilated stomach, with an annular ridge at its right extremity—the pylorus, a dilatation of the first part of the duodenum, and a stricture of the second part.

The father of this patient, a man of 63, had also had attacks of indigestion ever since 10 years of age, and had found no treatment useful except lavage, which he had carried out himself for the last fifteen years. He was in Guy's and then gave signs of great dilatation of the stomach, and brought up, from the stomach, at one time 5½ pints of foul fluid.

Dr. Wardrop Griffith thought it difficult to eliminate the scarring of an ulcer.

Dr. Hutchison said that congenital stricture of the duodenum was not so very rare. He had seen two specimens in the last year. The symptoms were the same as those of congenital pyloric stricture.

Dr. French asked why, if the disease was congenital, the symptoms should not have begun before 10 years of age.

Dr. Fawcett replied that the position and form of the stricture and the absence of thickening were strongly against cicatrix. He suspected that the symptoms had begun before the age stated.

3. Dr. French stated that at Guy's in cases of broncho-pneumonia after diphtheria he had found *B. diphth.* in the lungs and in the blood stream.

Dr. Symes stated that in Bristol they had found this also, but that the infection was usually mixed. He suggested that in such cases the antitoxin might be given by the intravenous method.

Dr. Claude Ker advised repeated injection of antitoxin for several days, and had seen such improvement in these cases that it seemed as if the preponderating infection must be diphtheria. Intravenous injection was in children both difficult and dangerous.

Dr. French replied that the Klebs-Loeffler bacillus preponderated, but that the infection was mixed.

During the midday interval—

1. Professor Graham Kerr demonstrated the objects of interest in the Biological Section of the Museum, including a series of Microscopic Preparations of Protozoa (the latter in the Zoological Laboratory).

2. Professor J. H. Teacher demonstrated William Hunter's Anatomical and Pathological Specimens.

3. The University Librarian showed certain rare Medical Books from the Hunterian Collection.

At the afternoon Session—

1. Drs. G. A. Gibson and W. T. Ritchie showed electro-cardiographic tracings of cases with presystolic murmurs. All showed the P. waves of auricular systole.
The paper was discussed by Dr. Phear and the President.

2. Dr. Ivy Mackenzie described the results of investigations of five hearts which had been clinically diagnosed by Mackenzie and Lewis as cases of auricular fibrillation. He had found muscular degeneration in the auricles and ascribed it to malnutrition from overwork and from loss of proper diastolic time for repair. He showed drawings.

Sir James Barr referred to work now in process at Cambridge and thought that the character of the blood, especially the absence of lime salts from it, probably played a large part in the phenomenon.

Dr. Alexander Morison laid stress upon the nerve supply and thought disorganization of nerves might have something to do with it.

Dr. Carey Coombs had found marked organic degeneration in both auricles. Digitalis provides diastolic rest, and is in these cases useful probably on that account.

Dr. Travers Smith remarked that in some cases auricular fibrillation is not incompatible with a comfortable life of many years' duration.

Dr. John Cowan thought there were two classes of auricular fibrillation which differed in their pathology. He pointed out that fibrosis of the heart may be due to many causes. But acute inflammation was certainly one cause of auricular fibrillation, as he had seen at least six cases in the last 100 of acute rheumatism.

Dr. Ritchie referred to paroxysmal attacks of auricular fibrillation. In the more permanent cases, fibrosis is very common. But is it the cause of fibrillation?—for it is very commonly found where there has been no fibrillation.

Dr. Hobhouse emphasized the division of these cases into two, the rapid or acute, which was dangerous, and the chronic such as Dr. Travers Smith referred to.

Dr. Ivy Mackenzie was doubtful of the importance of the chemical condition of the blood. He did not deny the nervous influence in these cases, but the question was, how was it exerted? The bundle of His is a specialized end organ, partly nervous and partly muscular. But in his cases no lesion of the bundle existed.

3. Dr. Alexander Morison showed micro-photographs of the heart wall from the pig and sheep in which large nerves were visible. He thought the condition of the nerves should be thoroughly examined in diseased human hearts. Hitherto microscopic examination of human hearts had been confined to cases of heart-block. A more extended series, including the normal, was needed. He showed two cases of fibrosis of the bundle of His without any heart-block during life, and pleaded that the nervous system should be thoroughly considered and not only the muscular tissue.

Dr. G. A. Gibson was in agreement.

Dr. Ivy Mackenzie referred to Gaskell's work on the myogenic function of the heart as the great classic from which all pathologists must start.

Dr. A. G. Gibson inquired as to the staining method employed.

Dr. Hay doubted the evidence that there was no heart-block in these cases. No jugular tracings were shown.

Dr. Morison replied.

4. Dr. Finlay showed a heart from a case of Stokes-Adams disease in which an aneurysm was found occupying the position of the *a–v* bundle. He was a man of 25. A tracing taken during one of the epileptiform attacks showed an auricular beat of 90 and a ventricular of 20. Towards the close of life the attacks became less frequent, and the pulse more frequent. He referred to Dr. Wardrop Griffith's case described at the Dublin Meeting, 1909.

Dr. Wardrop Griffith said that his case was almost exactly like this. In his case also the pulse became quicker towards the end. He thought it was possibly due to the lessening of the aortic and therefore of the aneurysmal pressure upon the bundle as the patient got weaker.

Dr. Morison also discussed the paper and Dr. Finlay replied.

5. Dr. Ritchie related the results of a series of experiments to see whether the function of the vagus as revealed by experiment in animals could be proved to exist in man. He had used atropine to paralyse, and pressure in the neck to stimulate, the vagus. The compression results were somewhat inconstant, but otherwise much resembled those obtained by stimulation in animals, whereas atropine gave opposite results.

Sir Clifford Allbutt asked how long a dose of atropine continued to show effect.

Dr. G. A. Gibson noticed how striking were this and the last paper as examples of the clinical application of physiology.

Dr. Wardrop Griffith said that in a case of his own $\frac{1}{50}$ grain of atropine began to produce an effect in three minutes, and continued to produce it for three hours.

Dr. Hume confirmed Dr. Griffith's observation.

On Friday, April 19, at 10 a.m. the Meeting resumed.

1. Dr. Owen Williams (and Miss Mildred Powell introduced) gave an account of a series of observations on the effect of diastase in diabetes. All had a normal amount of diastase in the saliva.

Diastase had no effect on N metabolism or on acid intoxication or on sugar excretion.

It produced a slight rise in phenolphthalein acidity. The observations began after a very successful case of von Noorden's treatment with oatmeal, and originated in an attempt to find out the cause of the action of oatmeal.

Dr. Drummond asked whether the author had given oatmeal during coma.

Dr. French asked (1) whether there were any statistics of the incidence of diabetes among the Scotch; (2) what dose of diastase was required to raise the acidity.

Dr. Williams replied that there is no difference in incidence between Scotch and other nations, but that von Noorden's method is to give oatmeal without any other ordinary protein, which would not be the case in any ordinary Scotch diet. He had not used oatmeal for coma, but Herrick had recommended it. The dose of diastase did not seem to make much difference in the rise of acidity.

Dr. Buckley and Dr. Cowan had both used oatmeal with good effect when symptoms of acid intoxication were present.

2. Dr. Hawthorne laid down the following propositions:

(1) In arterial sclerosis homonymous hemianopsia usually means unilateral intracranial vascular lesion.

(2) Homonymous hemianopsia occasionally occurs in circumstances which suggest intracranial vascular lesion in young women—probably thrombosis.

(3) These latter cases are certainly not functional.

Dr. James Taylor agreed that hemianopsia is never a symptom of hysteria. He had seen it several times as an isolated symptom in young women. He thought such cases almost certainly due to thrombosis.

Dr. Warrington inclined to arterial rather than venous or sinous thrombosis.

Dr. Risien Russell agreed with Dr. Warrington. He asked for information

regarding hemianaesthesia and the pupillary reaction, and reminded the meeting that haemorrhage occasionally occurs in young women.

Dr. Calwell raised the question of influenza as a cause of this symptom.

Dr. Harry Campbell mentioned that the macular region usually escapes in unilateral vascular lesions, whereas it was involved in Dr. Hawthorne's cases.

Dr. Hawthorne replied.

3. Dr. Byrom Bramwell related the case of a man aged 34, a jockey, in whom he had carried out extensive laminectomy and section of the VII to X posterior dorsal nerve roots for the relief of gastric crises of great frequency and severity. The operation had completely stopped the crises, and also the lightning pains. For the latter he could give no explanation.

Dr. Saundby had a similar case. The operation had stopped the crises, but myelitis and bed-sores had followed, and the man was on the whole rather worse than better.

Dr. James Taylor had never recommended it. The usual course of gastric crises was to improve. He thought Dr. Bramwell's case was very exceptional, and he would not like to take it as a guide.

Dr. Warrington and Dr. Stalker discussed the case.

Dr. Risien Russell suggested that part of the effect may have been due to laminectomy, which sometimes has a beneficial effect on meningitis.

Dr. Harry Campbell had treated one case by this operation for severe lightning pains, but without good effect.

Dr. Byrom Bramwell agreed that this treatment should always be the exception, but could not agree that gastric crises tended to spontaneous cure. In answer to Dr. Stalker he thought the patient free from any neurotic taint. There was no marked meningitis present, but he thought it likely that relief of pressure had some connexion with the cure of the pains.

4. Dr. Leonard Findlay (introduced) described and exhibited a case of Thomsen's disease. He quoted, and for the most part could repeat, the observations of Dr. Wardrop Griffith recently published. He noticed that reflex contraction produced by tapping the patellar tendon is not prolonged. Kreatinin was in excess in the urine. He inclined to a nervous origin for the disease.

Dr. Wardrop Griffith referred to the cases quoted.

Dr. Travers Smith related the case of an officer who had had it all his life but not so severely as to prevent him doing his duty.

5. Dr. Parsons described a method for the estimation of iodine which he thought might be of use in determining whether the thyroid was overactive. He had as yet made too few observations to speak positively.

Dr. Hutchison warned him that the iodine in the diet would have to be taken into account and might otherwise disturb the calculations.

6. Dr. W. MacLennan thought that the clinical varieties of ulcerative endocarditis were not easily separable and discussed the inefficiency of our means of diagnosis. (1) The fever was very variable. He thought, however, that in comparison with others it was remarkably benign in character. It was often intermittent. (2) The blood seldom gave growth on culture though organisms were easily found on the valves. Leucocytosis was often absent and there was even sometimes leucopenia. (3) The spleen was sometimes very large, without any infarction, but no certain prognosis could be made from this symptom.

Dr. French asked whether in leucopenia the polymorphonuclears are proportionately diminished.

Dr. Hawthorne did not think the fever was more benign than many others. He noted the absence of cardiac murmur in some cases.

Dr. MacLennan replied that by leucopenia he implied poverty of the polymorphonuclear cells.

At 12.30—Professor Muir gave a lecture on the changes in the blood experimentally produced by injecting haemolytic serum.

At 3 p.m.—

1. Dr. W. K. Hunter related two cases in which he had treated paroxysmal haemoglobinuria with Salvarsan. Both gave the Wassermann reaction before treatment. After treatment the one patient, a man aged 27, gave no Wassermann reaction, and had no further attacks though working in cold places. The other, a little girl aged 5, did not give a strongly negative Wassermann reaction after treatment. Eason's reaction was still present in her blood.

Dr. Carl Browning (introduced) described the Eason reactions given by the child's blood and showed the tubes.

2. Dr. Herringham drew the attention of the Association to certain unusual cases of haemoglobinuria which occurred—(1) in the course of rheumatism or pneumonia; (2) without known cause accompanied by local pain. He described cases.

3. Dr. Hutchison related a case of paroxysmal haemoglobinuria due to exertion in a man aged 17. It had begun during November last for no known cause. He also had functional albuminuria of the orthostatic form. When at rest his serum gave no haemolysis either with normal R. B. C. or with his own. After exertion his serum was haemolytic to normal R. B. C. but not, *in vitro*, to his own. After 10 c.c. horse serum had been given he entirely and permanently lost his functional albuminuria and for a few days his haemoglobinuria, but in the latter respect gradually returned to his previous condition. Another 10 c.c. horse serum were given, and the haemoglobinuria was now erratic and uncertain. Cold had no effect.

Dr. Drummond mentioned that in some cases the red cells were present in large numbers, which occasionally led to mistakes in diagnosis. He related one such.

Dr. Eason advised that the serum when obtained from the blood should be immediately centrifuged. It is much better to get it from a cantharides blister. He had had four cases since his last paper. All gave his reactions, but other authors had not always been able to get them. He thought the explanation was either that the serum had been left in contact with the cells, or that some of the cases were not typical.

Dr. Hobhouse had seen two cases of paroxysmal haemoglobinuria in children. One of them now has permanent albuminuria. He had seen a case of paroxysmal malarial haematuria.

Dr. Saundby said that Dr. Druitt never lost the tendency, but that some patients recover.

Dr. Bramwell confirmed Dr. Saundby. He had seen a case of paroxysmal haematuria due to cold.

Professor Muir remarked that you may be unable to show any effect *in vitro*, and yet *in vivo* it may be visible.

Dr. Hawthorne stated that albuminuria occasionally replaces haemoglobinuria.

The authors replied. Dr. Herringham stated his belief that paroxysmal haemoglobinuria was allied to some forms of functional albuminuria and that probably these cases shaded off into the natural.

4. Professor Hill Abram related the case of a man, aged 53, who died of haemochromatosis after an illness of four years. He thought it toxic in character.

Dr. Hay had seen the case in 1909, when the chief symptom was marked pigmentation of the face, neck, and hands. The liver was tender and very large and the blood pressure raised (180 mm. Hg.). The spleen was not palpable and the urine was natural. In March, 1910, the spleen was palpable. In May glycosuria began. From that time he steadily lost weight. Before death both liver and spleen had diminished.

Dr. Harry Campbell mentioned a case of his own.

Professor Muir showed specimens from two similar cases. One was not recognized till after death from suppurative peritonitis due to perforation. In that case the skin was not pigmented and the urine had not been obtained.

Dr. Drummond mentioned a case in which there was pigmentation and glycosuria ; but the enlargement of the liver was due to new growth which impinged on the pancreas.

Dr. Abram replied.

5. Dr. Byrom Bramwell related a series of cases of pernicious anaemia treated by Salvarsan.   In two of them there was an improvement which was very surprising, but in the rest this did not occur.

Dr. W. K. Hunter mentioned that syphilis should always be eliminated, as it gives a blood picture just like that of pernicious anaemia.

Dr. French, Dr. Warrington, and Dr. Calwell discussed the paper and Dr. Bramwell replied.   None of his cases were syphilitic.

6. Dr. Finlay exhibited specimens illustrating an extraordinary spread or metastases in a case of carcinoma of the breast.   Deposits were found in the skin, scalp, pleura, lung, heart, liver, kidney, ovary, ileo-caecal valve, brain, and choroid tunic of the eye.

Dr. Hawthorne referred to similar cases and suggested that the usual limitation of metastasis should rather surprise us, and should be ascribed to some condition inhibiting the growth which was natural to the cells when carried to distant parts of the blood.

Dr. Finlay replied.

A vote of thanks was passed to the University Court and to Professor Noel Paton for their courtesy and hospitality.